Clinical Study Protocol – Amendment No. 1

A SINGLE CENTER, SINGLE DOSE, OPEN-LABEL, RANDOMIZED, TWO PERIOD CROSSOVER PIVOTAL STUDY TO DETERMINE THE BIOEQUIVALENCE OF TWO FORMULATIONS CONTAINING HALOPERIDOL 2 MG IN HEALTHY MALES AND FEMALES UNDER FED CONDITIONS

FARMOVS STUDY NUMBER:	0145FRM18
SPONSOR STUDY NUMBER:	CT-006
TEST PRODUCT:	Haloperidol Tablets, 2 mg, Cycle Pharmaceuticals Ltd.
REFERENCE PRODUCT:	Haloperidol Tablets, USP, 2 mg, Mylan Pharmaceuticals Inc.
DEVELOPMENT PHASE:	Fed Bioequivalence Study
SPONSOR:	Cycle Pharmaceuticals Ltd.
STUDY CENTER:	FARMOVS Clinical Research Organisation
REGULATORY AUTHORITY:	Food and Drug Administration, United States
Original Protocol:	Final 1.0, 14 Aug 2019
Protocol Amendment No. 1:	Final 2.0, 25 Sep 2019
	NCT04411953

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PROTOCOL AMENDMENT NO 1 – SUMMARY OF CHANGES

At the request of the principal investigator, the clinical study protocol, Final 1.0, dated 14 Aug 2019 was amended as follows:

Changes and Reasons	Sections Affected
Text was adjusted to include magnesium and thyroid-stimulating hormone (TSH) safety tests to be done at screening, and magnesium safety tests to be done at the interim safety visit and post-study visit. Reason: Magnesium and TSH testing was erroneously omitted from the safety assessments in the protocol, Table 7-1 (Schedule of Study Assessments). These tests are required in order to apply Exclusion Criteria number 18 (Hypomagnesemia) and number 19 (Hypothyroidism or hyperthyroidism). The total blood volume to be collected during the study was not affected as these tests will be performed using the blood sample collected for clinical chemistry.	• Section 2 List of Abbreviations and Definitions of Terms • Table 7-1 Schedule of Study Assessments

SYNOPSIS

Title of the Study

A SINGLE CENTER, SINGLE DOSE, OPEN-LABEL, RANDOMIZED, TWO PERIOD CROSSOVER PIVOTAL STUDY TO DETERMINE THE BIOEQUIVALENCE OF TWO FORMULATIONS CONTAINING HALOPERIDOL 2 MG IN HEALTHY MALES AND FEMALES UNDER FED CONDITIONS

Study Objectives

Primary Objective

To determine whether the test product, Haloperidol Tablets, 2 mg (Cycle Pharmaceuticals Ltd.), and the reference product, Haloperidol Tablets, USP, 2 mg (Mylan Pharmaceuticals Inc.) are bioequivalent.

Secondary Objective

To evaluate the safety and tolerability of Haloperidol Tablets, 2 mg in healthy males and females.

Study Design

The study will comprise:

- a screening period of maximum 21 days,
- two treatment periods (each of which will include a profile period of 192 hours) separated by a wash-out period of at least 14 calendar days (minimum number of days based on half-life of the analyte) between consecutive administrations of the investigational product (IP),
- an interim visit 2 days before admission to Treatment Period 2, and
- a post-study visit will be performed when the subjects attend the last PK sampling visit (192 hours post-dose), or within 72 hours after the subject withdrew/was withdrawn from the study.

Procedures listed for the post-study visit will be performed in the event of early withdrawal from the study.

Subjects will be assigned randomly to treatment sequence, before the first administration of IPs.

In-house Stay

Subjects will be admitted to the study center on Day -1 and will remain in the study center for at least 24 hours after dosing. Subjects have to return to the study center for the subsequent blood sample collections up to 192 hours after dosing.

Pharmacokinetic Sampling Times

Pharmacokinetic (PK) blood samples will be collected at the following time points: at pre-dose (0 hours), at 30 minutes, at 1 hour, 1 hour 30 minutes, 2 hours, 2 hours 30 minutes, 3 hours, 3 hours 30 minutes, 4 hours, 4 hours 30 minutes, 5 hours, 5 hours 30 minutes, 6 hours, 8 hours, 12 hours, 16 hours, 24 hours, 30 hours, 36 hours, 48 hours, 72 hours, 96 hours, 120 hours, 144 hours, 168 hours and 192 hours post-dose (total: 26 samples per treatment period).

Blood Volume

If genetic screening is not performed, the total blood volume to be collected from each subject during the study is about 235 mL (repeat laboratory investigations are not included). If genetic screening is performed, the total blood volume to be collected from each subject during this study is about 245 mL (repeat laboratory investigations are not included).

The total blood volume to be collected from each subject during this study is less than the volume given as a single donation at the South African Blood Transfusion Service (i.e., 480 mL).

Study Population

Subjects who meet all the inclusion criteria and none of the exclusion criteria will be considered eligible to participate in the study.

Inclusion Criteria

1. Healthy males and females, 18 to 55 years (both inclusive) at the time of signing of informed consent.
2. Body mass index (BMI) between 18.5 and 30 kg/m^2 (both inclusive).
3. Body mass not less than 50 kg.
4. Medical history, vital signs, physical examination, standard 12-lead electrocardiogram (ECG) and laboratory investigations must be clinically acceptable or within laboratory reference ranges for the relevant laboratory tests, unless the investigator considers the deviation to be irrelevant for the purpose of the study.
5. Non-smokers.
6. Females, if:
   - Not of childbearing potential, e.g., has been surgically sterilized, undergone a hysterectomy, amenorrhea for ≥ 12 months and considered post-menopausal,

     Note: In post-menopausal women, the value of the serum pregnancy test may be slightly increased. This test will be repeated to confirm the results. If there is no increase indicative of pregnancy, the female will be included in the study.
   - Of childbearing potential, the following conditions are to be met:
     – Negative pregnancy test

       If this test is positive, the subject will be excluded from the study. In the rare circumstance that a pregnancy is discovered after the subject received IP, every attempt must be made to follow her to term.
     – Not lactating
     – Abstaining from sexual activity (if this is the usual lifestyle of the subject) or must agree to use an accepted method of contraception, and agree to continue with the same method throughout the study

     An example of a reliable method of contraception is a non-hormonal intrauterine device.

     In this study the concomitant use of hormonal contraceptives is NOT allowed.

     Other methods, if considered by the investigator as reliable, will be accepted.
7. Written consent given for participation in the study.
8. Written consent given for participation in the genetic component of the study (if performed based on Food and Drug Administration [FDA] feedback). If the subject declines participation in the genetic component, the subject will not be allowed to participate in the study.
9. Subjects must be willing to consume the meal prescribed before administration of the IP in full and within the required time.

Exclusion Criteria

1. Evidence of psychiatric disorder, antagonistic personality, poor motivation, emotional or intellectual problems likely to limit the validity of consent to participate in the study or limit the ability to comply with protocol requirements.
2. Current alcohol use > 21 units of alcohol per week for males and > 14 units of alcohol per week for females (1 unit is equal to approximately 330 mL of beer, one small glass [200 mL] of wine, or one measure [25 mL] of spirits).
3. Regular exposure to substances of abuse (other than alcohol) within the past year.
4. Use of any medication, prescribed or over-the-counter or herbal remedies, within 2 weeks before the first administration of IP except if this will not affect the outcome of the study in the opinion of the investigator.

   In this study the concomitant use of hormonal contraceptives is NOT allowed.
5. Participation in another study with an experimental drug, where the last administration of the previous IP was within 8 weeks (or within 5 elimination half-lives for chemical entities or 2 elimination half-lives for antibodies

or insulin, whichever is the longer) before administration of IP in this study, at the discretion of the investigator.

6. Treatment within the previous 3 months before the first administration of IP with any drug with a well-defined potential for adversely affecting a major organ or system.
7. A major illness during the 3 months before commencement of the screening period.
8. History of hypersensitivity or allergy to the IP or its excipients or any related medication.
9. History of hypersensitivity or allergy to the pre-medication or its excipients or any related medication.
10. History of hypersensitivity or allergy to the rescue medication or its excipients or any related medication.
11. History of bronchial asthma or any other bronchospastic disease.
12. History of convulsions.
13. History of porphyria.
14. History of cardiac arrhythmias.
15. History of sudden cardiac death in the family or history of familial long QT syndrome.
16. Relevant history or laboratory or clinical findings indicative of acute or chronic disease, likely to influence study outcome.
17. Cytochrome P450 (CYP) 2D6 poor metabolizers (if warranted by the FDA).
18. Hypomagnesemia.
19. Hypothyroidism or hyperthyroidism.
20. Hypokalemia.
21. Subjects with narrow-angle glaucoma.
22. Subjects with stenosing peptic ulcers.
23. Subjects who have pyloroduodenal obstruction.
24. Subjects who have symptomatic prostatic hypertrophy or bladder-neck obstruction.
25. Known or previous dystonia or dyskinesia.
26. Subjects with severe toxic central nervous system depression or who have experienced comatose states from any cause.
27. Subjects who have Parkinson's disease.
28. Donation or loss of blood equal to or exceeding 500 mL during the 8 weeks before the first administration of IP.
29. Diagnosis of hypotension made during the screening period.
30. Diagnosis of hypertension made during the screening period or current diagnosis of hypertension.
31. Resting pulse of > 100 beats per minute or < 40 beats per minute during the screening period, either supine or standing.
32. Positive testing for human immunodeficiency virus (HIV), hepatitis B and hepatitis C.
33. Positive urine screen for drugs of abuse. In case of a positive result the urine screen for drugs of abuse may be repeated once at the discretion of the investigator.
34. Positive pregnancy test (female subjects).
35. Hemoglobin count deviating more than 10% of the lower limit of normal.
36. Veins unsuitable for venous blood collection.
37. Difficulty in swallowing.
38. Any specific IP safety concern.
39. Vulnerable subjects, e.g., persons in detention.
40. Employees or close relatives of the contract research organization, the sponsor, 3rd party vendors or affiliates of the above mentioned parties.

Pre-medication

Generic name:	Benztropine mesylate
Trade name:	Benztropine Mesylate Tablets, USP
Dosage form and strength:	1 mg tablet
Study dose:	1 mg (1 tablet) every 10 to 12 hours, beginning 4 to 6 hours before dosing, for a total of 4 doses
Route of administration:	Oral
Manufacturer:	[redacted]
Country of origin:	United States of America

Rescue Medication

Generic name:	Diphenhydramine hydrochloride
Trade name:	Diphenhydramine Hydrochloride Injection, USP
Dosage form and strength:	50 mg/mL
Study dose:	50 mg (up to 100 mg, but not exceeding a daily dose of 400 mg)
Route of administration:	Intravenous or intramuscular
Manufacturer:	[redacted]
Country of origin:	United States of America

Investigational Products

Reference Product (Treatment A)

Generic name:	Haloperidol
Trade name:	Haloperidol Tablets, USP
Dosage form and strength:	2 mg tablets
Study dose:	2 mg (1 tablet)
Route of administration:	Oral
Manufacturer:	Mylan Pharmaceuticals Inc.
Country of origin:	United States of America

Test Product (Treatment B)*

Generic name:	Haloperidol
Dosage form and strength:	2 mg tablets
Study dose:	2 mg (1 tablet)
Route of administration:	Oral
Manufacturer:	Cycle Pharmaceuticals Ltd. [redacted]
Country of origin:	United Kingdom

Analyte

Haloperidol

* The sample used in this study is from a production batch.

Sample Size

Up to 32 eligible subjects will be enrolled in the study to complete the study with at least 24 evaluable subjects.

Pharmacokinetic Parameters

Primary PK Parameters for Haloperidol:

- Maximum observed plasma concentration (C_{max})
- Area under the plasma concentration versus time curve, from time zero to t, where t is the time of the last quantifiable concentration ($AUC_{(0-t)}$)
- Area under the plasma concentration versus time curve, with extrapolation to infinity ($AUC_{(0-\infty)}$)

Secondary PK Parameters for Haloperidol:

- Time to maximum observed plasma concentration (t_{max})
- Terminal elimination rate constant (λ_z)
- Apparent terminal elimination half-life ($t_{½}$)

The following statistical information for C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ will be provided: Geometric means, arithmetic means, geometric means ratios, 90% confidence intervals (CIs).

Safety Variables

Safety variables will include reporting of adverse events (AEs), vital signs, physical examination, 12-lead electrocardiogram (ECG) and laboratory investigations (hematology, clinical chemistry, urinalysis and pregnancy tests). Prior and concomitant medication will also be recorded.

Statistical Analysis

Pharmacokinetic population: All subjects who complete the PK sampling in all periods and for whom primary PK parameters can be calculated for all treatment periods, and who have no major protocol deviations thought to impact the analysis of the PK data will be included in the statistical PK analysis of the study.

Bioequivalence of the test and reference products will be assessed on the basis of the 90% CIs for estimates of the geometric mean ratios between the primary PK parameters (C_{max}, $AUC_{(0-t)}$, $AUC_{(0-\infty)}$) of the test and reference products using an analysis of variance (ANOVA) considering the conventional bioequivalence range of 80.00% to 125.00%.

Safety population: All subjects who received at least one dose of IP will be included in the safety analysis of the study.

Safety data will be listed and summarized as appropriate.

Demographic characteristics and AEs will be summarized by treatment.

SIGNATURE: SPONSOR SIGNATORY / SIGNATORIES

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FARMOVS STUDY NUMBER:	0145FRM18
SPONSOR STUDY NUMBER:	CT-006

I hereby declare that I have reviewed this clinical study protocol

[redacted]

CEO

Cycle Pharmaceuticals Ltd.

[redacted]

Cycle Pharmaceuticals Ltd.

[redacted]

STATEMENT AND SIGNATURE: PRINCIPAL INVESTIGATOR

A SINGLE CENTER, SINGLE DOSE, OPEN-LABEL, RANDOMIZED, TWO PERIOD CROSSOVER PIVOTAL STUDY TO DETERMINE THE BIOEQUIVALENCE OF TWO FORMULATIONS CONTAINING HALOPERIDOL 2 MG IN HEALTHY MALES AND FEMALES UNDER FED CONDITIONS

FARMOVS STUDY NUMBER:	0145FRM18
SPONSOR STUDY NUMBER:	CT-006

I, the undersigned, verify that, to the best of my abilities and knowledge:

1. I have reviewed this clinical study protocol and approve its contents.
2. I am familiar with the properties of the investigational medicinal product as described in the Introduction and References section of this clinical study protocol. I am qualified by scientific training and experience to conduct the clinical investigational study identified above. My medical education and experience is stated in the curriculum vitae provided.
3. The study center has adequate study staff and appropriate facilities (including laboratories) that will be available for the duration of the study to be conducted in conformance with this clinical study protocol and Good Clinical Practices (including the South African Clinical Trials guidelines), as assured by an "in-house" quality assurance program.
4. I agree to obtain permission from the sponsor in writing should any changes be required to the clinical study protocol. Should the safety of the subjects necessitate immediate action, which represents a deviation from the clinical study protocol, the sponsor will be informed as soon as possible.
5. I shall obtain in writing the necessary approval from the independent ethics committee (IEC) and the South African Health Products Regulatory Authority (SAHPRA). I shall ensure communication of any modification, amendment or deviation of the clinical study

protocol, and also inform the IEC and the SAHPRA in the event of discontinuation of the study and the reasons for discontinuation.

6. I agree to obtain written informed consent from all potential subjects before performance of any study-related activity. Subject study information will be provided in a language that the potential subject understands.

7. I shall ensure that case report forms are completed, signed and archived at the study center as applicable.

8. I agree to allow the auditor/inspector/any representatives of regulatory authorities and IEC access to all relevant documents and be available to discuss any findings/issues.

9. I shall ensure that the confidentiality of all information about subjects is respected by all persons involved, as well as information supplied by the sponsor. Any disclosure of such information will only be made subject to the sponsor's written approval.

10. I agree to render a clinical study report of my findings after the end of this study, suitable for regulatory purposes, whether or not the study has been completed.

11. In my absence one of the sub-investigators, approved for participation in this study, will act as principal investigator for study-related decisions.

1. TABLE OF CONTENTS

1.1. List of Tables

1.2. List of Figures

2. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Adverse event reporting	Adverse events will be documented as such only from the time that the investigational product (IP) has been administered. Events experienced before that time will be regarded as part of the subject's medical history.
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANOVA	Analysis of Variance
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration versus time curve
$AUC_{(0-t)}$	AUC, from time zero to t, where t is the time of the last quantifiable concentration
$AUC_{(0-\infty)}$	AUC, with extrapolation to infinity
β-HCG	Beta human chorionic gonadotropin
BASD	FARMOVS Bioanalytical Services Division
BLQ	Below the limit of quantification
BMI	Body mass index
CDER	Center for Drug Evaluation and Research
CI	Confidence interval
Citrus fruits	Any of numerous fruits of the genus *Citrus* e.g., orange, lemon, lime, grapefruit and tangerine
C_{max}	Maximum observed plasma concentration
CNS	Central nervous system
Completer	Enrolled subject who completes the entire study
Concomitant medication	Any medication given in addition to the IP
CRF	Case report form
CS	Clinically significant (abnormalities)
CSP	Clinical study protocol
CSR	Clinical study report
CV%	Coefficient of variation percentage
CYP	Cytochrome P450

CYP3A4, CYP2D6	Enzyme(s) produced from cytochrome P450 genes that are involved in the metabolism of haloperidol
DMP	Data management plan
ECG	Electrocardiogram
ECS	Edit Check specifications
EDTA	Ethylenediaminetetraacetic acid
EMA	European Medicines Agency (established 1995)
End of study	Last subject's last visit
Enrolled subject	Person allocated a subject number which confirms formal entry into the study
EU	European Union / European Community
FARMOVS	FARMOVS Clinical Research Organisation, Bloemfontein, South Africa
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase (transpeptidase)
GLP	Good Laboratory Practice
Hb	Hemoglobin
HCT	Hematocrit
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Council for Harmonisation
ICH E3	ICH guideline for structure and content of clinical study reports
IEC	Independent ethics committee
In-house day	Time ranging from the start of the profile period until discharge from the study center
IP	Investigational product
ISO/IEC	International Organisation for Standardisation/International Electrotechnical Commission
λ_z	Terminal elimination rate constant
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
LLOQ	Lower limit of quantification
MCHC	Mean corpuscular hemoglobin concentration
MCH	Mean corpuscular hemoglobin

MCV	Mean corpuscular volume
n	Number of subjects/observations
NCS	Not clinically significant (abnormalities)
Non-qualifier	Subject not included in the study due to ineligibility during the screening period, or an eligible subject who became ineligible before allocation of a subject number (e.g., due to illness and/or use of medication)
NS	No sample
Non-smoker	Subject who has not smoked previously and/or has not used nicotine or nicotine-containing products for at least 3 months; subjects who have discontinued smoking or the use of nicotine/nicotine-containing products (including snuff and similar products) at least 3 months before the first administration of the IP
OECD	Organisation for Economic Cooperation and Development
Participant/Subject	The terms “subject” and “participant” are considered synonymous and used interchangeably.
PGx	Pharmacogenetic sampling
PK	Pharmacokinetic(s)
Profile period	Pharmacokinetic blood sampling period, including in-house stay
RBC	Red blood cell
Refuser	Eligible subject who withdraws before being allocated a subject number
Replacement	Eligible subject who enters the study to replace a subject who withdrew or was withdrawn from the study
SAE	Serious adverse event
SAHPRA	South African Health Products Regulatory Authority
SANAS	South African National Accreditation System
SAP	Statistical analysis plan
Screening period	Time window during which potential subjects are evaluated to establish eligibility for enrollment into the study
SD	Standard deviation
SOC	System organ class
SOP	Standard operating procedure
SST	Serum separator tube
Standby	A subject (screened within the required time period before the first administration of the IP, considered eligible but not enrolled as the

	required number of subjects for enrollment has been met) available as a replacement
Study start	Study start is defined as administering or giving directions for the administration of the IP to a subject for the purposes of this study
SUSAR	Suspected unexpected serious adverse reaction
$t_{½}$	Apparent terminal elimination half-life
t_{max}	Time to maximum observed plasma concentration
TSH	Thyroid-stimulating hormone
Treatment period	Time between the first and last study-related procedures of a period of IP administration
Wash-out period	Period between consecutive administrations of IP
WBC	White blood cell
Withdrawal	Enrolled subject who is withdrawn by the investigator before the clinical phase of the study has been completed

3. ETHICS

3.1. Mandatory Approvals and Protocol Amendments

Written approval for the final version of the clinical study protocol (CSP) and any amendments (if applicable), as well as other applicable documents will be obtained from an independent ethics committee (IEC) and the South African Health Products Regulatory Authority (SAHPRA) before performance of any study-related procedures.

Independent Ethics Committee

[redacted]

This protocol is to be followed exactly. Amendments must be written to alter the protocol. However, in the event of any medical emergency, the investigator is free to institute any medical procedure he/she deems appropriate. Such events and procedures must be reported promptly to the sponsor.

In the event of a protocol amendment, study documents not affected by the amendment that have already been prepared, will not necessarily be updated to reflect the date of the amendment.

Amendments will be made available to study protocol recipients.

3.2. Ethical Conduct of the Study

The study will be conducted in compliance with this CSP and ethical principles that have their origins in the Declaration of Helsinki, including the following guidelines:

- Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa, Department of Health, South Africa, 2006.
- International Council for Harmonisation (ICH) Harmonised Guideline, Integrated Addendum to ICH E6(R1), Guideline for Good Clinical Practice (GCP) E6(R2), Step 5, dated 09 November 2016.

3.3. Subject Information and Informed Consent

Before commencement of the screening procedures, the potential subjects will be informed verbally by the investigator and in writing by way of the informed consent form (ICF) concerning the nature, purpose and risks involved in the screening procedures as well as the purpose, procedures, restrictions, obligations, remuneration, insurance coverage and possible adverse drug reactions relevant to the study.

The purpose of the study, the procedures to be carried out and the potential hazards will be described to the potential subjects in non-technical terms. Potential subjects will be required to read, sign and date the ICF before enrollment. They will be assured that they may withdraw from the study at any time without jeopardizing their medical care. Each potential subject will be given a signed copy of the ICF.

The original as well as any revision of the ICF provided to the subjects will be submitted for ethics approval.

Representative written information for the subjects and sample consent forms will be kept in the Investigator Site File.

3.3.1. Confidentiality

Study data will be stored in accordance with local and global data protection laws. Information on confidentiality is also contained in the ICF.

Potential subjects will be informed that representatives of the sponsor, IEC, regulatory authorities or auditors may inspect their medical records to verify the information collected, and

that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

The investigator will maintain a subject identification list (subject numbers with the corresponding subject names) to enable records to be identified. All communications and documents relevant to subjects in the study will identify each person by the subject's study number only.

3.3.2. Remuneration of Subjects

Compensation will be reasonable and related to the nature and degree of inconvenience and discomfort as a result of participation in the study. Information on how subjects will be compensated is contained in the ICF.

3.3.3. Indemnity

Insurance cover has been arranged to indemnify the subjects in the event of death or any deterioration in health or well-being caused by participation in the study.

The certificate of insurance will be kept in the Investigator Site File.

4. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Principal Investigator

[redacted]

Study Staff and Other Services

Information on the sub-investigators and other persons whose participation will materially affect the conduct of the study, including third party service providers, is contained in the Investigator Site File.

Study Center

FARMOVS Clinical Research Organisation

[redacted]

Routine Safety and Analytical Laboratory

FARMOVS Bioanalytical Services Division (BASD)

[redacted]

Sponsor

Cycle Pharmaceuticals Ltd.

[redacted]

Sponsor Medical Expert

For the purposes of this study, the principal investigator will fulfil the role of medical expert.

Sponsor Contact Person

[redacted]

Monitor

Information on the monitor to the study is contained in the Investigator Site File.

5. INTRODUCTION

5.1. Background Information

Haloperidol is the first of the butyrophenone series of major tranquilizers. [1]

Haloperidol is a high potency first-generation antipsychotic and one of the most frequently used antipsychotic medications used worldwide. While haloperidol has demonstrated pharmacological activity at a number of receptors in the brain, it exerts its antipsychotic effect through its strong antagonism of the dopamine receptor (mainly D2), particularly within the mesolimbic and meocortical systems in the brain. While the exact mechanism is not entirely understood haloperidol is known to inhibit the effects of dopamine and increase its turnover. Traditional antipsychotics, such as haloperidol binds more tightly than dopamine itself to the dopamine D2 receptor, with dissociation constants that are lower than that for dopamine. It is believed that haloperidol competitively blocks post-synaptic dopamine (D2) receptors in the brain, eliminating dopamine neurotransmission and leading to the relief of delusions and hallucinations that are commonly associated with psychosis. [2] At recommended doses, haloperidol had low alpha-1 antiadrenergic activity and no antihistaminergic or anticholinergic activity. [3]

Haloperidol is indicated for use in the management of manifestations of psychotic disorders. It is also indicated for the control of tics and vocal utterances of Tourette's Disorder in children and adults. Haloperidol tablets are effective for the treatment of severe behavior problems in children of combative, explosive hyperexcitability (which cannot be accounted for by immediate provocation). Haloperidol tablets are also effective in the short-term treatment of hyperactive children who show excessive motor activity with accompanying conduct disorders consisting of some or all of the following symptoms: impulsivity, difficulty sustaining attention, aggressivity, mood lability, and poor frustration tolerance. Haloperidol tablets should be reserved for these two groups of children only after failure to respond to psychotherapy or medications other than antipsychotics. [1]

5.2. Clinical Pharmacokinetics

Absorption:

Haloperidol is a highly lipophilic compound and is extensively metabolized in humans, which may cause a large inter-individual variability in it pharmacokinetics (PK). [2]

The average bioavailability of haloperidol after administration of the tablet or oral solution is 60% to 70%. [3] Studies have found a wide variance in PK values for orally administered haloperidol with peak plasma levels of haloperidol are generally attained within 2 to 6 hours, 14.5 to 36.7 hours reported for half-life ($t_{½}$) and 43.73 µg/L•h (range 14.89 to 120.96 µg/L•h) reported for AUC. [2, 3] A high inter-subject variability in plasma concentrations was observed. Steady-state is reached within 1 week of treatment initiation. [3]

Distribution:

Mean haloperidol plasma protein binding in adults is approximately 88 to 92%. There is a high inter-subject variability for plasma protein binding. Haloperidol is rapidly distributed to various tissues and organs, as indicated by the large volume of distribution (mean values 8 to 21 L/kg after intravenous dosing), which also suggests free movement through various tissues including the blood-brain barrier. It also crosses the placenta and is excreted in breast milk. [2, 3]

Metabolism:

Haloperidol is extensively metabolised in the liver. The main metabolic pathways of haloperidol in humans include glucuronidation, ketone reduction, oxidative N-dealkylation and formation of pyridinium metabolites. [2, 3] In psychiatric patients treated regularly with haloperidol, the concentration of haloperidol glucuronide in plasma is the highest among the metabolites, followed, in rank order, by unchanged haloperidol, reduced haloperidol and reduced haloperidol glucuronide. [2] The metabolites of haloperidol are not considered to make a significant contribution to its activity; however, the reduction pathway accounts approximately for 23% of the biotransformation, and back-conversion of the reduced metabolite of haloperidol to haloperidol cannot be fully ruled out. [2, 3] The enzymes involved in the biotransformation of haloperidol include cytochrome P450 (CYP) including CYP3A4 and CYP2D6, carbonyl reductase and uridine di-phosphoglucose glucuronosyltransferase enzymes. The greatest proportion of the intrinsic hepatic clearance of haloperidol is performed by glucuronidation and followed by the reduction of haloperidol to reduced haloperidol and by CYP-mediated oxidation. [2] In studies of cytochrome-mediated disposition *in vitro*, CYP3A4 appears to be the major isoform of the enzyme responsible for the metabolism of haloperidol in humans. The intrinsic clearance of the back-oxidation of reduced haloperidol to the parent compound, oxidative N-dealkylation and pyridinium formation are of the same order of magnitude. This suggests that the same enzyme system is responsible for the above three metabolic reactions. [2] Inhibition or

induction of CYP3A4, or inhibition of CYP2D6, may affect haloperidol metabolism. A decrease in CYP2D6 enzyme activity may result in increased haloperidol concentrations. [2, 3]

Elimination:

The terminal elimination half-life of haloperidol is on average 24 hours (range of means 15 to 37 hours) after oral administration. Haloperidol apparent clearance after extravascular administration ranges from 0.9 to 1.5 L/h/kg and is reduced in poor metabolisers of CYP2D6. [3]

Reduced CYP2D6 enzyme activity may result in increased concentrations of haloperidol. The inter-subject variability (coefficient of variation, %) in haloperidol clearance was estimated to be 44% in a population pharmacokinetic analysis in patients with schizophrenia. [2, 3] After intravenous haloperidol administration, 21% of the dose was eliminated in the faeces and 33% in the urine. Less than 3% of the dose is excreted unchanged in the urine. [3]

Genetic polymorphism of CYP2D6 has been demonstrated to be an important source of inter-patient variability in the PK of haloperidol and may affect therapeutic response and incidence of adverse effects. [2]

Age effect:

Haloperidol is not approved for the treatment of patients with dementia-related psychosis. [1]

5.3. Adverse Events, Contraindications and Warnings

Refer to the Product Information presented in Appendix 15.3. As with any medication, the list of adverse events (AEs) will never be exhaustive, and unexpected or very rare AEs not listed could potentially occur.

5.4. Study Rationale

The sponsor has developed a generic formulation (test product) of an existing medication (reference product) which is intended for marketing authorization.

The proposed study in healthy males and females is designed to establish a PK profile under fed conditions for the orally administered test and reference products to evaluate bioequivalence in accordance with the following guidelines:

- United States Department of Health and Human Services, Food and Drug Administration (FDA) Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally

Administered Drug Products - General Considerations. Center for Drug Evaluation and Research (CDER) March 2003 BP.

- United States Department of Health and Human Services, Food and Drug Administration (FDA) Guidance for Industry: Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA, Draft Guidance. Center for Drug Evaluation and Research (CDER), December 2013 Biopharmaceutics.
- United States Department of Health and Human Services, FDA Guidance for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies, CDER, December 2002 BP.

5.4.1. Justification for Study Design

The design and conduct of this clinical study is based on standard requirements for bioequivalence studies contained in applicable guidelines (see Section 5.4).

Based on FDA recommendation, bioequivalence of the test and reference product will be evaluated under fed (Study CT-006) and fasting (Study CT-005) conditions as per Guidance for Industry, Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA, posted December 2013. As per this Guidance, when a fasting *in vivo* bioequivalence study is recommended for an orally administered, immediate release product, it is recommended that a fed study be conducted, except when the dosage and administration section of the reference product labeling states that the product should be taken only on an empty stomach (e.g., the labeling states that the product should be administered 1 hour before or 2 hours after a meal). For Haloperidol Tablets, 2 mg, USP, the label does not state administration 1 hour before or 2 hours after a meal and therefore a fed bioequivalence study was recommended.

A randomized crossover design has been chosen to minimize the effects of between-subject variability and any period effects on the overall results.

5.5. Risks and Benefits

Safety measures are instituted to closely monitor subject safety during this clinical study and to assess known risks of the investigational product (IP).

Haloperidol should be used with caution in subjects known to be CYP2D6 poor metabolizers (approximately 10% of the population) [3]. Following dosing, these subjects are likely to have high concentrations of the parent compound compared to moderate and/or extensive metabolizers. At the time of writing of this protocol, further discussions were ongoing with the

FDA regarding poor metabolizers. Based on FDA feedback, and in order to ensure subject safety, the sponsor may decide to perform genetic screening to identify subjects who are poor metabolizers prior to dosing. Based on FDA feedback, the sponsor may decide to exclude poor metabolizers from the study.

To prevent severe dystonia, subjects will be pre-medicated with benztropine mesylate tablets, 1 mg every 10 to 12 hours beginning 4 to 6 hours before dosing with haloperidol and continuing for a total of 4 doses to provide coverage during periods of substantial haloperidol levels. In the event of breakthrough acute dystonia, diphenhydramine hydrochloride 50 mg (but not exceeding a daily dose of 400 mg) could be administered intramuscular or intravenous.

Healthy subjects enrolled in the clinical study will not benefit directly from participation in the study as treatment of illnesses is not the objective. It is foreseen that the information gained during the clinical study will contribute towards the treatment of patients for conditions for which this product is indicated.

6. STUDY OBJECTIVES

Primary Objective

To determine whether the test product, Haloperidol Tablets, 2 mg (Cycle Pharmaceuticals Ltd.), and the reference product, Haloperidol Tablets, USP, 2 mg (Mylan Pharmaceuticals Inc.) are bioequivalent.

For this purpose the PK profile of haloperidol will be compared after administration of a single dose of 2 mg of each of the two formulations, under fed conditions.

Secondary Objective

To evaluate the safety and tolerability of Haloperidol Tablets, 2 mg in healthy males and females.

Refer to Section 11.4 and Section 9 for primary and secondary parameters/variables (endpoints).

7. INVESTIGATIONAL PLAN

Bias will be prevented by strict adherence to the inclusion and exclusion criteria, the use of a randomization schedule and application of the particular study design. All measurement procedures are clearly defined in advance, and will be applied consistently and precisely.

7.1. Overall Study Design and Plan: Description

7.1.1. Study Design

This will be a single dose, open-label, laboratory-blind, randomized, two period crossover study with orally administered haloperidol 2 mg conducted under fed conditions in at least 24 healthy males and females at a single study center.

The study will comprise of:

- a screening period of maximum 21 days;
- two treatment periods (each of which will include a profile period of 192 hours) separated by a wash-out period of at least 14 calendar days (minimum number of days based on half-life of the analyte) between consecutive administrations of the IP;
- an interim visit 2 days before admission to Treatment Period 2, and
- a post-study visit will be performed when the subjects attend the last PK sampling visit (192 hours post-dose) or within 72 hours after the subject withdrew/was withdrawn from the study.

Procedures listed for the post-study visit will be performed in the event of early withdrawal from the study.

Subjects will be assigned randomly to treatment sequence, before the first administration of IP.

7.2. Discussion of Study Design

7.2.1. Treatment Periods and Schedule of Study Assessments

Details and timing of assessments are displayed in Table 7-1.

The time of dosing commencement may vary for logistical reasons. Actual clock times will vary between subjects, in relation to actual dosing times.

The flow of events is illustrated in Figure 7-1 for all treatments.

Figure 7-1 Study Flow Chart

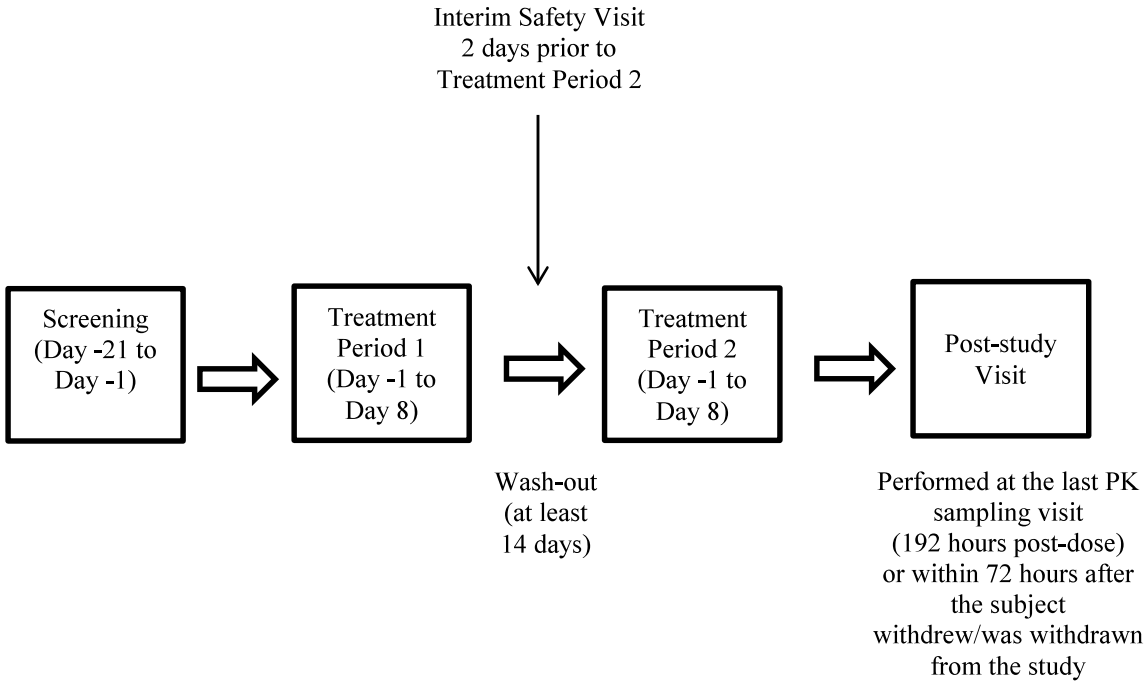


Table 7-1 Schedule of Study Assessments

Assessment	Screening	Admission	Treatment Period 1	Interim Safety Visit[1]	Admission	Treatment Period 2	Post-study Visit[2]
Informed consent	X						
Demographic and anthropometric data[3]	X						
Alcohol and tobacco consumption patterns	X						
Medical and medications history[4]	X	X					
Adverse events and concomitant medication			X	X	X	X	X
Physical examination[5]	X						
Vital signs[6]	X		X			X	
12-Lead ECG[7]	X		X			X	X
Hematology[8]	X			X			X
Clinical chemistry[9]	X			X			X
Serology tests[10]	X						
Urinalysis[11]	X						
Pregnancy test[12] (female subjects only)	X	X			X		X
Urine screen for drugs of abuse[13]	X	X			X		
Urine cotinine screen for tobacco use[14]	X						
Alcohol breath test[15]	X	X			X		
Randomization			X				
PGx screening[16]	X						
Pre-medication administration[17]			X			X	
IP administration			X			X	
PK profile[18]			X			X	

ECG = electrocardiogram; IP = investigational product; PK = pharmacokinetic

1. Two days before admission to Treatment Period 2.
2. Performed when the subjects attend the last PK sampling visit (192 hours post-dose) or, in the case of a subject who took the IP and was withdrawn or withdrew, within 72 hours of withdrawal/withdrawing from the study.
3. Sex, race, date of birth, age, height and body weight.
4. The recorded medical history will be updated if necessary on admission to Treatment Period 1.
5. A full physical examination will include the following: Evaluation for jaundice, pallor (anemia), cyanosis, clubbing, edema and lymphadenopathy; skin evaluation; fundoscopy; ear, nose and throat; cardiovascular assessment; respiratory assessment; abdominal evaluation; musculoskeletal assessment; neurological assessment; other evaluations may be performed as deemed necessary by the investigator. This will be commented upon in the clinical study report, if applicable.
6. Supine and standing systolic and diastolic blood pressure and pulse will be recorded at screening. Supine blood pressure and pulse will be recorded before administration of IP; in addition, supine blood pressure and

pulse will be recorded at 2, 4 and 6 hours post-dose. Body temperature will be recorded at screening and before administration of IP (either standing or supine).

7. Standard 12-lead ECG will be performed at screening, at 4 hours post-dose and at post-study.
8. Hematology (Ethylenediaminetetraacetic acid [EDTA tubes]): white blood cell (WBC) count, red blood cell (RBC) count, hemoglobin (Hb), hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), absolute differential count (neutrophils, lymphocytes, monocytes, eosinophils and basophils) and platelets. Blood samples will be collected for interim safety hematology evaluations 2 days prior to admission for Treatment Period 2.
9. Clinical chemistry (Serum separator tubes [SST]): Potassium, sodium, urea, creatinine, uric acid, calcium, protein, albumin, total bilirubin, alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), magnesium and glucose. Blood samples will be collected for interim safety clinical chemistry evaluations 2 days prior to admission for Treatment Period 2.
   Screening only: Thyroid-stimulating hormone (TSH).
10. Tests for human immunodeficiency virus (HIV), hepatitis B and hepatitis C, performed using commercially available test kits. Pre- and post-test counseling will be provided as appropriate.
11. Urinalysis (dipstick): Glucose, bilirubin, ketones, specific gravity, blood, pH, protein, urobilinogen, nitrite and leucocytes. Abnormal urinalysis results may be repeated at the discretion of the investigator.
12. Serum pregnancy test (quantitative β-HCG [beta human chorionic gonadotropin] method) at screening. On admission to each treatment period urine pregnancy testing will be performed. If any of these tests are positive, persons will not be allowed further participation in the study. Urine pregnancy test at post-study.
13. Using a rapid, one-step screening test for simultaneous, qualitative detection of multiple drugs and drug metabolites, such as amphetamines, barbiturates, benzodiazepines, cocaine, opiates, phencyclidine, tetrahydrocannabinol, methadone, methamphetamine, tricyclic antidepressants, oxycodone and propoxyphene. Subjects with alleged false positive test results will be excluded from the study. However, a positive test may be repeated once at the discretion of the investigator.
14. Cotinine testing using commercially available testing procedures.
15. Alcohol breath test using a portable breath alcohol measuring device. The test will be performed at screening, on admission to each treatment period and at random. If any of these tests are positive, persons will not be allowed further participation in the study.
16. Based on FDA feedback, a blood sample may be taken for genetic screening in order to identify CYP2D6 poor metabolizers. Based on FDA feedback, the sponsor may decide to exclude poor metabolizers from the study.
17. Administration of pre-medication beginning 4 to 6 hours before administration of IP. Pre-medication to be given at 10 to 12-hour intervals for 4 doses.
18. Pharmacokinetic (PK) blood samples will be collected at the following time points: at pre-dose (0 hours), at 30 minutes, at 1 hour, 1 hour 30 minutes, 2 hours, 2 hours 30 minutes, 3 hours, 3 hours 30 minutes, 4 hours, 4 hours 30 minutes, 5 hours, 5 hours 30 minutes, 6 hours, 8 hours, 12 hours, 16 hours, 24 hours, 30 hours, 36 hours, 48 hours, 72 hours, 96 hours, 120 hours, 144 hours, 168 hours and 192 hours post-dose (total: 26 samples per treatment period). The collection of PK blood samples take precedence over other assessments at a scheduled time point.

7.2.2. Safety and Data Monitoring Committees

No safety and data monitoring committee will be established for this study.

7.2.3. Interim Analyses

Interim analyses of safety data will be performed as indicated in Table 7-1.

7.2.4. Expected Duration of Study

The duration of this study is expected to be approximately 24 days per subject (excluding the screening period). The actual overall study duration and study recruitment time may vary.

7.2.5. Pre-study Evaluation (Screening)

Within 21 days before the first administration of IP and after written informed consent was obtained, screening procedures will be performed on each potential subject (see Table 7-1). Subjects who meet the inclusion criteria (Section 7.3.1) will be considered eligible to participate in the study. Subjects who meet one or more of the exclusion criteria (Section 7.3.2) will not be considered eligible to participate in the study.

At the discretion of the investigator, vital signs and laboratory investigations of variables outside the reference ranges may be repeated up to three times. Should the variables return to within the reference range, or should the investigator consider the variable to be at an acceptable level in relation to the reference range, the persons will be considered eligible to participate in the study.

If the sponsor decides to perform genotyping, based on discussions with the FDA, subjects will be asked to sign a separate ICF for the collection of a blood sample for genetic testing. This sample will be used to determine if the subject is a CYP2D6 poor metabolizer. If the subject declines to participate in the genetic component of this study, he/she will not be allowed to participate in the study. The sponsor will decide, based on ongoing discussions with the FDA, whether or not to exclude CYP2D6 poor metabolizers from the study.

7.2.6. Treatment Periods

Each treatment period will include a profile period of 192 hours, which will commence with morning dosing of IP on a 24-hour clinic stay at the study center. Subjects will be admitted to the study center on Day -1 to ensure an overnight fast of at least 10 hours before dosing.

Subjects will receive pre-medication (1 mg every 10 to 12 hours), beginning 4 to 6 hours before dosing with IP and continuing for a total of 4 doses.

Before dosing, an indwelling venous cannula will be inserted. The registered nurse will decide when to remove or replace the venous cannula based on the time (since insertion of the cannula) or if clotting occurs. If the cannula is removed, the subsequent blood samples will be collected by venipuncture or the cannula will be replaced.

The IP will be administered in the standing position. Refer to Section 7.2.10.1.

Food and beverages on clinic days will be according to Section 7.2.10.2.

Subjects will remain in the study center for at least 24 hours after dosing, providing they agree to return for the subsequent blood sample collection up to 192 hours post-dose as instructed by the study staff.

7.2.7. Post-study Evaluations

See Table 7-1.

At the discretion of the investigator, a post-study physical examination will be performed on subjects withdrawn from the study due to an AE.

Post-study laboratory investigations with variables outside the reference ranges will not necessarily be repeated to establish if and when those variables returned to within the reference ranges. The variables will be reviewed against the clinical background, other relevant investigations and their relevance to the administered IP, before a decision will be taken to repeat the investigations in question. At the discretion of the investigator, the investigations of certain variables outside the reference ranges may be repeated until the variables return to within the reference range for the particular laboratory test, or until the investigator considers the repeated variable to be at an acceptable level in relation to the reference range. If the investigator has made every effort to contact the subject, but he/she remains unavailable to attend the clinic for repeat of applicable laboratory investigations, the investigator may declare him/her lost to follow-up, according to FARMOVS standard operating procedures (SOPs).

In cases where results of post-study evaluations are reported after the database has been locked, the results will be handled according to the relevant FARMOVS SOPs and the applicable clinical laboratory reports will be presented in the appendices to the clinical study report (CSR).

7.2.8. Sampling, Interim Handling and Storage

7.2.8.1.Safety Blood and Urine Samples

Refer to Table 7-1.

Before starting the study, the investigator (or designee) will supply the sponsor and applicable study staff with the reference ranges and units of measurement for the laboratory safety variables

to be used during the study. If the reference ranges change during the course of the study, the investigator (or designee) must provide the sponsor and applicable study staff with a list of the new reference ranges and the effective dates.

All safety blood and urine sampling will be performed by the study center, according to FARMOVS SOPs.

The principal investigator or designee will ensure that all biological fluids collected during the study will not be used for purposes other than as directed by the CSP. All collected biological fluids used for safety investigations will be destroyed according to FARMOVS SOPs.

7.2.8.2. Pharmacokinetic Blood Samples

Pharmacokinetic blood samples will be collected as indicated in Table 7-1. The actual blood sampling times will be documented.

Venous blood samples, 4 mL each, for the determination of plasma haloperidol concentrations will be collected into labeled, dipotassium ethylenediaminetetraacetic acid plastic tubes.

Blood samples are routinely placed on ice between sample collection and centrifuging. Within 1 hour of collection, centrifuging of blood samples will commence at approximately 2700 g within a range of 0°C to 8°C for 10 minutes. Thereafter, the supernatant of each sample will be divided into 2 aliquots (of at least 0.9 mL plasma each), transferred to labeled, plastic tubes and frozen.

All sample tube labels will contain at least the following information: study number, analyte, time (protocol time and/or relative sampling time), subject number, blood sample number and treatment period. Plasma samples will be stored at approximately -20°C in a temperature monitored freezer until transfer to BASD. Pooled samples for concentration range estimation will be prepared according to FARMOVS SOPs. These samples for range estimation originate from some of the blood samples collected for drug assays and may be used by the analytical laboratory to determine suitable quantification ranges.

Unused duplicate plasma PK samples will be stored at BASD for up to 6 months after completion of the bioanalysis phase of the study. The sponsor will be notified when the 6 months storage period has elapsed and will be required to indicate in writing whether additional storage is needed or whether the samples may be discarded.

7.2.8.3. Genetic Screening: CYP2D6 Poor Metabolizers

Following ongoing discussions with the FDA, the sponsor may decide to perform genetic screening in order to identify CYP2D6 poor metabolizers. If the sponsor decides to perform genetic screening, a blood sample (up to 10 mL) will be collected from each subject during screening. This sample will be analyzed by a FARMOVS approved third party vendor who specializes in genetic analysis of samples. Details of the third party vendor will be included in the Investigator Site File and the CSR (if the analysis is performed). The process implemented for the analysis of genetic samples will be discussed in a separate Laboratory Manual.

7.2.9. Blood Volume

7.2.9.1.Blood Volume: Excluding Genetic Screening

If genetic screening is not performed, the total blood volume to be collected from each subject during the study is about 235 mL (repeat laboratory investigations are not included), which is less than the volume given as a single donation at the South African Blood Transfusion Service (i.e., 480 mL) (Table 7-2).

Table 7-2 Total Blood Volume to be Collected during the Study (Excluding PGx Screening)

Assay	Volume per sample (mL)	Total number of samples	Total blood volume (mL)
Haloperidol	4	26 x 2	208
Hematology	4	3	12
Clinical chemistry*	5	3	15
Total blood volume (entire study)**			235

* Serum pregnancy tests (females only) and serology tests at screening will be performed on the sample collected for clinical chemistry

** Excluding repeat laboratory investigations

7.2.9.2.Blood Volume: Including Genetic Screening

If genetic screening is performed, the total blood volume to be collected from each subject during the study is about 245 mL (repeat laboratory investigations are not included), which is less than the volume given as a single donation at the South African Blood Transfusion Service (i.e., 480 mL) (Table 7-3).

Table 7-3 Total Blood Volume to be Collected during the Study (Including PGx Screening)

Assay	Volume per sample (mL)	Total number of samples	Total blood volume (mL)
Haloperidol	4	26 x 2	208
Hematology	4	3	12
Clinical chemistry*	5	3	15
PGx screening	10	1	10
Total blood volume (entire study)**			245

* Serum pregnancy tests (females only) and serology tests at screening will be performed on the sample collected for clinical chemistry

** Excluding repeat laboratory investigations

7.2.10. General and Dietary Restrictions

7.2.10.1. Posture

The pre-medication will be administered either in the standing or sitting position, after which no restrictions concerning posture or movement will apply (applicable only to dosing with pre-medication).

The IP will be administered in the standing position. Following dosing with the IP, subjects will be required to sit upright on the edge of their beds for 20 minutes and to lie on their right side for the remainder of the first hour. Except for bladder voiding, dosing of pre-medication and ingestion of meals (where applicable), subjects will remain recumbent until 8 hours after administration of study medication, after which no restrictions concerning posture or movement will apply. Posture control procedures will be documented.

7.2.10.2. Diet

The ingestion of food and beverages containing citrus fruits and/or apple or pineapple will not be allowed for 72 hours before the administration of IP and until the last PK blood sample is collected per treatment period.

The ingestion of food and beverages containing alcohol and/or methylxanthines e.g., caffeine (coffee, tea and cola) will not be allowed for 24 hours before the administration of IP and until the last PK blood sample is collected per treatment period.

Food and beverage intake during the clinic stay will be standardized per treatment period. Meals taken after dosing will be standardized in regard to composition and time of administration and it will be documented.

Water is allowed as desired except for 1 hour before and 1 hour after IP administration and no food is allowed for at least 4 hours post-dose and 10 hours pre-dose (except for the high-fat, high-calorie breakfast) served prior to dosing.

A high-fat, high-calorie breakfast will be served 30 minute before administration of the IP (see Appendix 15.1 for the fat and energy content). The whole meal must be consumed within 30 minutes and the IP should be administered 30 minutes after start of the meal.

Food and beverage intake will be allowed *ad libitum*, unless restrictions apply, after the subjects have been discharged from the clinic.

7.2.10.3. Physical Activity

Strenuous physical activity will not be allowed for 24 hours before the administration of IP and until the last PK blood sample was collected per treatment period.

7.2.10.4. Special Precautions

Subjects will be informed verbally and in writing of the AEs that they may experience after taking the IP. At discharge, they will be requested to sign a form stating that they undertake not to drive a motorized vehicle, operate any machinery or perform a hazardous task for the following 24 hours (see Appendix 15.2).

7.3. Selection of Study Population

The criteria are set to ensure a homogeneous subject population without accompanying diseases that may interfere with the conduct and scientific evaluation of the study. Additionally, the criteria have been selected to minimize risk to the subjects' well-being.

7.3.1. Inclusion Criteria

1. Healthy males and females, 18 to 55 years (both inclusive) at the time of signing of informed consent.
2. Body mass index (BMI) between 18.5 and 30 kg/m^2 (both inclusive).
3. Body mass not less than 50 kg.

4. Medical history, vital signs, physical examination, standard 12-lead electrocardiogram (ECG) and laboratory investigations must be clinically acceptable or within laboratory reference ranges for the relevant laboratory tests, unless the investigator considers the deviation to be irrelevant for the purpose of the study.

5. Non-smokers.

6. Females, if:

   - Not of childbearing potential, e.g., has been surgically sterilized, undergone a hysterectomy, amenorrhea for ≥ 12 months and considered post-menopausal,

     Note: In post-menopausal women, the value of the serum pregnancy test may be slightly increased. This test will be repeated to confirm the results. If there is no increase indicative of pregnancy, the female will be included in the study.

   - Of childbearing potential, the following conditions are to be met:

     – Negative pregnancy test

       If this test is positive, the subject will be excluded from the study. In the rare circumstance that a pregnancy is discovered after the subject received IP, every attempt must be made to follow her to term.

     – Not lactating

     – Abstaining from sexual activity (if this is the usual lifestyle of the subject) or must agree to use an accepted method of contraception, and agree to continue with the same method throughout the study

       An example of a reliable method of contraception is a non-hormonal intrauterine device.

       In this study the concomitant use of hormonal contraceptives is NOT allowed.

       Other methods, if considered by the investigator as reliable, will be accepted.

7. Written consent given for participation in the study.

8. Written consent given for participation in the genetic component of the study (if performed based on FDA feedback). If the subject declines participation in the genetic component, the subject will not be allowed to participate in the study.

9. Subjects must be willing to consume the meal prescribed before administration of the IP in full and within the required time.

7.3.2. Exclusion Criteria

1. Evidence of psychiatric disorder, antagonistic personality, poor motivation, emotional or intellectual problems likely to limit the validity of consent to participate in the study or limit the ability to comply with protocol requirements.
2. Current alcohol use > 21 units of alcohol per week for males and > 14 units of alcohol per week for females (1 unit is equal to approximately 330 mL of beer, one small glass [200 mL] of wine, or one measure [25 mL] of spirits).
3. Regular exposure to substances of abuse (other than alcohol) within the past year.
4. Use of any medication, prescribed or over-the-counter or herbal remedies, within 2 weeks before the first administration of IP except if this will not affect the outcome of the study in the opinion of the investigator.

   In this study the concomitant use of hormonal contraceptives is NOT allowed.
5. Participation in another study with an experimental drug, where the last administration of the previous IP was within 8 weeks (or within 5 elimination half-lives for chemical entities or 2 elimination half-lives for antibodies or insulin, whichever is the longer) before administration of IP in this study, at the discretion of the investigator.
6. Treatment within the previous 3 months before the first administration of IP with any drug with a well-defined potential for adversely affecting a major organ or system.
7. A major illness during the 3 months before commencement of the screening period.
8. History of hypersensitivity or allergy to the IP or its excipients or any related medication.
9. History of hypersensitivity or allergy to the pre-medication or its excipients or any related medication.
10. History of hypersensitivity or allergy to the rescue medication or its excipients or any related medication.
11. History of bronchial asthma or any other bronchospastic disease.
12. History of convulsions.
13. History of porphyria.

14. History of cardiac arrhythmias.
15. History of sudden cardiac death in the family or history of familial long QT syndrome.
16. Relevant history or laboratory or clinical findings indicative of acute or chronic disease, likely to influence study outcome.
17. Cytochrome P450 (CYP) 2D6 poor metabolizers (if warranted by the FDA).
18. Hypomagnesemia.
19. Hypothyroidism or hyperthyroidism.
20. Hypokalemia.
21. Subjects with narrow-angle glaucoma.
22. Subjects with stenosing peptic ulcers.
23. Subjects who have pyloroduodenal obstruction.
24. Subjects who have symptomatic prostatic hypertrophy or bladder-neck obstruction.
25. Known or previous dystonia or dyskinesia.
26. Subjects with severe toxic central nervous system depression or who have experienced comatose states from any cause.
27. Subjects who have Parkinson's disease.
28. Donation or loss of blood equal to or exceeding 500 mL during the 8 weeks before the first administration of IP.
29. Diagnosis of hypotension made during the screening period.
30. Diagnosis of hypertension made during the screening period or current diagnosis of hypertension.
31. Resting pulse of > 100 beats per minute or < 40 beats per minute during the screening period, either supine or standing.
32. Positive testing for human immunodeficiency virus (HIV), hepatitis B and hepatitis C.
33. Positive urine screen for drugs of abuse. In case of a positive result the urine screen for drugs of abuse may be repeated once at the discretion of the investigator.
34. Positive pregnancy test (female subjects).

35. Hemoglobin count deviating more than 10% of the lower limit of normal.
36. Veins unsuitable for venous blood collection.
37. Difficulty in swallowing.
38. Any specific IP safety concern.
39. Vulnerable subjects, e.g., persons in detention.
40. Employees or close relatives of the contract research organization, the sponsor, 3rd party vendors or affiliates of the above mentioned parties.

7.3.3. Withdrawal Criteria

Subjects have the right to withdraw from the study at any time, irrespective of the reason, without detriment to their medical care.

The following are pre-defined incidents that may lead to withdrawal from further participation:

1. Adverse events as a result of the IP, at the discretion of the investigator.
2. Intercurrent illness requiring medication. The decision whether or not to withdraw the subject will be at the discretion of the investigator and will depend on the nature of the illness and medication used.
3. Protocol violation by subjects, at the discretion of the investigator. Protocol violation is defined as the willful disobeying of protocol instructions which have been communicated to the subjects verbally and in writing.
4. Pathologically raised body temperature before IP administration on profile days.
5. Positive testing for pregnancy (female subjects).
6. Positive testing for drugs of abuse.
7. Positive testing for cotinine.
8. Positive alcohol breath test.
9. Vomiting within 2 x median t_{max} of the reference product (t_{max} = 2 to 6 hours).
10. If the subject did not complete the meal prescribed before administration of the IP in full or within the required time limit.

The primary reason for treatment discontinuation will be documented.

If the investigator withdraws a subject from the study, the investigator will inform the subject verbally of this decision as well as post-study procedures to be followed to ensure subject safety. If the investigator withdraws a subject from treatment or if a subject declines further participation, a post-study visit will be completed for those who were exposed to IP, within 72 hours of withdrawal/withdrawing from the study.

If a subject's reason for discontinuation is an AE, this must be reported in accordance with the procedures detailed in Section 12. The investigator must make every effort to contact a subject, according to FARMOVS SOPs, before he/she can be regarded as lost to follow-up.

7.3.4. Replacement of Subjects

Subjects who withdraw or are withdrawn from the study will not be replaced, unless fewer complete the study than the estimated number of evaluable subjects (see Section 11.1).

If a subject is replaced, the replacement will be allocated the subject number of 500 plus the subject number being replaced (e.g., Subject 02 will be replaced by 502). The subject numbers being replaced will be selected such that the replacement subjects receive the same treatment sequence as the withdrawn subjects and the sequence balance is maintained.

7.3.5. Premature Termination of the Study

The sponsor or the investigator has the right to terminate the study at any time for medical and/or administrative reasons. As far as possible, this should occur after mutual consultation.

Criteria for termination include, but are not limited to, the fact that there are not enough subjects in the study, the study has reached the required number of subjects, or if the study is stopped by the sponsor.

If the study is prematurely terminated for any reason, the investigator will promptly inform the sponsor and the subjects and will ensure appropriate therapy and follow-up for them. The IEC and the SAHPRA will be informed as soon as possible after the decision has been made to terminate the study and the reasons for termination.

Should the study be prematurely terminated, the completed and partially completed case report forms (CRFs) and remaining IP must be returned to the sponsor.

8. TREATMENTS

8.1. Products to be Administered

Subjects will receive either the test or reference product, according to the randomization schedule, under fed conditions. Subjects will receive each product once.

Subjects will be pre-medicated with benztropine mesylate tablets, 1 mg every 10 to 12 hours beginning 4 to 6 hours before dosing with haloperidol and continuing for a total of 4 doses to provide coverage during periods of substantial haloperidol levels. The start time for administration of the pre-medication will be recorded in the individual subject CRFs. The pre-medication will be administered with 240 mL of water. In the event of breakthrough acute dystonia, diphenhydramine hydrochloride 50 mg (but not exceeding a daily dose of 400 mg) could be administered intramuscular or intravenous.

8.2. Pre-medication

Generic name:	Benztropine mesylate
Trade name:	Benztropine Mesylate Tablets, USP
Dosage form and strength:	1 mg tablet
Study dose:	1 mg (1 tablet) every 10 to 12 hours, beginning 4 to 6 hours before dosing, for a total of 4 doses
Route of administration:	Oral
Manufacturer:	[redacted]
Country of origin:	United States of America

8.3. Rescue Medication

Generic name:	Diphenhydramine hydrochloride
Trade name:	Diphenhydramine Hydrochloride Injection, USP
Dosage form and strength:	50 mg/mL
Study dose:	50 mg (up to 100 mg, but not exceeding a daily dose of 400 mg)
Route of administration:	Intravenous or intramuscular
Manufacturer:	[redacted]
Country of origin:	United States of America

8.4. Identity of Investigational Products

Reference Product (Treatment A)

Generic name:	Haloperidol
Trade name:	Haloperidol Tablets, USP
Dosage form and strength:	2 mg tablets
Study dose:	2 mg (1 tablet)
Route of administration:	Oral
Manufacturer:	Mylan Pharmaceuticals Inc.
Country of origin:	United States of America

Test Product* (Treatment B)

Generic name:	Haloperidol
Dosage form and strength:	2 mg tablets
Study dose:	2 mg (1 tablet)
Route of administration:	Oral
Manufacturer:	Cycle Pharmaceuticals Ltd. [redacted]
Country of origin:	United Kingdom

8.4.1. Identification of Investigational Products

The sponsor will conduct drug identification, content assay and dissolution tests for the test product, and if possible, for the reference product. Certificates of analysis will be provided in the CSR.

8.4.2. Supply and Storage

The sponsor will supply sufficient quantities of both products suitably packed for random selection of IP for dosing. The sponsor will also supply the pre-medication and rescue medication. The principal investigator or designee will ensure that the IPs are stored in a limited access area according to the storage instructions of the label, the information in the literature or instructions supplied by the sponsor.

* The sample used in this study is from a production batch.

8.4.3. Investigational Product Accountability

The principal investigator or designee will ensure that records of the receipt and administration of the IP are kept and that the IP will not be used for purposes other than as directed by the CSP. Once the clinical phase of the study has been completed or prematurely terminated, and after drug accountability has been performed, remaining IPs will be handled in accordance with sponsor requirements.

8.4.4. Retention Samples

The sponsor will provide a sufficient quantity of the test and reference products to be retained as retention samples at FARMOVS Bloemfontein, in accordance with the FDA Guidance for Industry – Handling and Retention of BA and BE Testing Samples, May 2004.

8.4.5. Labeling and Packaging

The FARMOVS pharmacist/designee, as designee of the principal investigator, will label, pack and randomize individual dose units if the IP is sent in bulk by the sponsor.

Investigational product to be administered at the study center on clinic days will be retained in a single separate container for each subject for each dose and product.

8.5. Method of Assigning Subjects to Treatment Groups

A randomization schedule will be provided by Biostatistics. The randomization schedule will be generated utilizing the PROC PLAN procedure of SAS® software or appropriate equivalent.

Subjects will be randomized to one of two treatment sequences (AB or BA) and will be assigned randomization numbers 01 – 32, sequentially.

Possible replacements will be handled according to Section 7.3.4.

Blinding is described in Section 8.8.

8.6. Selection of Doses in the Study

In compliance with bioequivalence guidelines, the dosage in this study will include a single oral dose of haloperidol 2 mg (as 1 tablet), on each of two separate occasions, under fed conditions. The dose administered is recommended for adults (18 – 55 years) for the treatment of moderate symptomatology of psychotic disorders.

See Section 5 and Appendix 15.3.

8.7. Selection and Timing of Dose for Each Subject

Pre-medication (and rescue medication, if required) will be administered with 240 mL of water.

After an overnight fast of at least 10 hours, subjects will receive a standardized high-fat, high-calorie breakfast 30 minutes before administration of IP. The entire meal must be consumed within 30 minutes and the IP should be administered 30 minutes after start of the meal. After completion of the breakfast subjects will receive either the reference or the test product (according to the randomization schedule) with 240 mL water. The tablet of haloperidol should be swallowed whole with water (see administration instructions in Product Information).

See also Section 5 and Section 7.2.6.

8.8. Blinding

This is an open-label, laboratory-blind study.

The principal investigator or designee will ensure that only assigned study staff members will have access to the randomization schedule. Laboratory personnel will not be allowed access to the randomization schedule.

8.9. Prior and Concomitant Medication

Subjects must refrain from using any medication, prescribed or over-the-counter (including herbal remedies and St. John's Wort [*Hypericum perforatum*]), for 2 weeks before the first administration of IP and for the duration of the study.

In this study the concomitant use of hormonal contraceptives is NOT allowed.

Concomitant administration of haloperidol is contraindicated as indicated in the Product Information provided in Appendix 15.3. Haloperidol is further contraindicated as discussed below.

Haloperidol is contraindicated in combination with medicinal products known to prolong the QTc interval. Caution should be used when haloperidol is used in combination with medicinal products known to cause electrolyte imbalance. Haloperidol is metabolized by several routes. Therefore caution should be used when haloperidol is administered in combination with medicinal products that may increase haloperidol plasma concentrations (including CYP3A4

inhibitors, CYP2D6 inhibitors, combined CYP3A4 and CYP2D6 inhibitors, and products for which the mechanism of action is unsure e.g., buspirone) or that may decrease haloperidol plasma concentrations. Haloperidol can increase the central nervous system (CNS) depression produced by alcohol or CNS-depressant medicinal products, including hypnotics, sedatives or strong analgesics. An enhanced CNS effect, when combined with methyldopa, has also been reported. Haloperidol may antagonize the action of adrenaline and other sympathomimetic medicinal products and reverse the blood pressure-lowering effects of adrenergic-blocking medicinal products. Haloperidol may antagonize the effect of levodopa or other dopamine agonists. Haloperidol is an inhibitor of CYP2D6. Haloperidol inhibits the metabolism of tricyclic antidepressants, thereby increasing plasma concentrations of these medicinal products. Caution should be used when haloperidol is administered in combination with lithium. Antagonism of the effect of the anticoagulant phenindione has been reported. [3]

The administration of concomitant medication will be handled on a case-by-case basis at the discretion of the investigator. If any medication is required during the course of the study, it must immediately be reported to the investigator. Where medication is taken or needs to be taken, a decision whether to continue or discontinue the subject's participation in the study will be based on safety concerns, the time of medication administration and the possible influence of the ingested medication on the PK of the IP and interference with the assay method.

8.10. Treatment Compliance

On admission to each treatment period, subjects are required to fill in a checklist in which they need to confirm that they adhered to the restrictions of the study. If they did not adhere to one or more of the study restrictions, the subjects will be withdrawn from the study, at the discretion of the investigator. These documents form part of the source documents for the study.

The pre-medication will be administered by the principal investigator or designee. A mouth check will be performed after each dosing of pre-medication by the principal investigator or designee to ensure that the subjects have swallowed the IP.

To ensure treatment compliance, the IP will be administered by the principal investigator or designee. A mouth check will be performed after each dosing by the principal investigator or designee to ensure that the subjects have swallowed the IP.

9. PHARMACOKINETIC PARAMETERS AND SAFETY VARIABLES

9.1. Pharmacokinetic and Safety Measurements

Refer to Section 7.2.1 for specific assessments and measurements, and the schedule of performance.

9.2. Appropriateness of Measurements

Standard measures to assess PK and safety apply during the study (see Table 7-1).

As this is a bioequivalence study, the planned safety measurements are considered adequate because the reference product is a marketed product that has extensive safety data and a known safety profile. It is not expected that the pharmacology, non-clinical and clinical properties of the text product would be different from those of the marketed reference product.

9.3. Drug Concentration (Pharmacokinetic) Measurements

9.3.1. Pharmacokinetic Parameters

Refer to Section 11.4.

9.3.2. Pharmacokinetic Sample Collection, Sample Handing and Storage

Refer to Section 7.2.8.2.

9.3.3. Pharmacokinetic Drug Assays

Following an inspection by the South African National Accreditation System (SANAS) conducted in January 2006, the analytical laboratories of BASD was granted a certificate for Good Laboratory Practice (GLP) compliance, based on the Organisation for Economic Cooperation and Development (OECD) guidelines ENV/MC/CHEM (98)17 as revised in 1997. Subsequent GLP inspections have all had successful outcomes. These inspections have confirmed that BASD is able to successfully apply GLP principles in studies that are performed at BASD. Various analytical methods have been validated by the BASD previously according to internationally accepted standards (as per including the European Medicines Agency [EMA] and FDA guidelines for Bioanalytical Method Validation). The quality and integrity of the analytical work generated in this study will be evaluated according to the acceptance criteria, as described in the SOPs of BASD and relevant internationally accepted standards.

Quantitative analysis of haloperidol in the collected plasma samples will be performed by BASD using liquid chromatography with tandem mass spectrometry (LC-MS/MS).

The pure substance with a certificate of analysis of haloperidol will be supplied by the sponsor or BASD will purchase pure substance of haloperidol from trustworthy supplier on behalf of the sponsor. This pure substance will be used as an analytical standard for the preparation of calibration standards and quality controls that are required for the quantitative analysis of haloperidol.

All the samples received at BASD, including samples of subjects who withdraw/are withdrawn, will be analyzed. Bioanalytical data will be processed according to the relevant SOPs of BASD.

A bioanalytical protocol will be written for this study and complete method validation and bioanalytical reports will be compiled and provided to the sponsor.

9.4. Safety Variables

Safety variables will include reporting of AEs, vital signs, physical examination, 12-lead ECG and laboratory investigations (hematology, clinical chemistry, urinalysis and pregnancy tests). Prior and concomitant medication will also be recorded.

10. DATA QUALITY ASSURANCE AND DATA MANAGEMENT

A study initiation meeting chaired by the principal investigator or designee will be held before study commencement.

A list of FARMOVS SOPs governing operating procedures described in this protocol will be contained in the Investigator Site File.

10.1. Quality Control and Source Data Verification

Source data verification will be conducted with due regard to subject confidentiality.

The site will allow the study monitor and sponsor representatives direct access to all study documents, medical files, and source documents to enable verification of the study data, whilst maintaining the anonymity of the subject and confidentiality of the data.

Internal quality control will be performed at all stages of the study by the study center.

10.2. Audit/Inspections

The investigator site, facilities and all data and documentation may be audited/inspected by independent auditor/inspector/any representatives of regulatory authorities and IEC. The investigator must allow the auditor/inspector/any representatives of regulatory authorities and IEC access to all relevant documents and be available to discuss any findings/issues. An audit certificate will be included in the CSR if an audit was performed.

10.3. Study Monitoring

The conduct of the study will be monitored by a representative of the sponsor to ensure compliance with applicable regulatory requirements and GCP. The summary of the documentation of the monitoring visits will form part of the study documentation and will be archived as such.

10.4. Data Collection

This study will use paper-based CRFs. The entries will be checked by trained personnel. Errors or inconsistencies will be corrected.

Any changes or corrections to a CRF will be dated, initialed and explained (if necessary) and will not obscure the original entry (e.g., correction fluid or covering labels must not be used). An explanation for the omission of any required data will appear on the appropriate page.

The investigator will sign the completed CRF, thereby taking responsibility for the accuracy of the data in the entire CRF. The investigator will retain records of the changes and corrections.

Source data will be defined as such in the Source Data Agreement.

The responsible study monitor will check data at the monitoring visits to the study center (see Section 10.3). The investigator will ensure that the data collected are accurate, complete and legible.

All clinical work conducted under this CSP is subjected to GCP regulations. These include an inspection by the sponsor and regulatory authority representatives at any time. The investigator will agree to the inspection of study-related records by regulatory authority and IEC representatives and to audits of the sponsor or third parties named by the sponsor (also see Section 10.2).

10.5. Data Management

Data Management will utilize standardized and validated procedures and systems to collect, process, and file the clinical data of this study. Any system used will be compliant with FDA 21 CFR Part 11 requirements.

A data management plan (DMP) will be prepared to describe the work and data-flow within the clinical study. Sponsor-specific requests, timelines, versions for the computer systems and the coding will be defined in the DMP.

Appropriate data validation checks may be developed based on the data sources. Edit Check Specifications (ECS) will be created for standard checks and custom checks. The ECS must be finalized and approved before data validation.

The paper-based CRFs will be scanned and transferred to Data Management after the data had been monitored, and receipt of all transferred CRFs will be logged.

Data will be entered from completed paper CRFs into the clinical database by double data entry. Electronic source data will be imported into a validated system (e.g., SAS) and reconciled with

the clinical database data. Only trained study staff will have access to the clinical database and every change in data will have a full audit trail.

The raw data intended for further processing will be checked by standard routines or according to the study ECS and queries will be generated and sent in the data cleaning log to the investigator for response. Appropriate corrections to the data will be made based on the responses provided on the data cleaning log. This process will be repeated until no further discrepancies are found. The data will then be declared clean. Applicable documentation will be stored in the study files.

11. STATISTICAL METHODS

11.1. Determination of Sample Size

Based on a bioequivalence range of 80.00% to 125.00% for C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$, a within-subject CV% of 22.5%, and a "test/reference" mean ratio between 0.95 and 1.05, 24 subjects are needed to achieve a power of 80% at an alpha level of 0.05 to show bioequivalence [4, 5].

Up to 32 eligible subjects will be entered into the study to complete the study with at least 24 evaluable subjects.

11.2. Statistical Methodology

The statistical methodology below describes the statistical analysis as it is foreseen when the study is being planned. A Statistical Analysis Plan (SAP) will be prepared with more details on the planned statistical methodology.

If circumstances should arise during the study rendering the analysis inappropriate, or if in the meantime improved methods of analysis should come to light, different analyses may be made. Any deviations from the statistical methodology, reasons for such deviations and all alternative or additional statistical analyses that may be performed, will be described in the CSR.

See SAP for a list of Tables, Figures and Listings to be appended in the CSR.

11.2.1. Rules for Handling Decimals

Refer to SAP for details.

11.2.2. Pharmacokinetic Population

All subjects who complete the PK sampling in all periods and for whom primary PK parameters can be calculated for all treatment periods, and who have no major protocol deviations thought to impact the analysis of the PK data will be included in the statistical PK analysis for the study.

Data from subjects who experienced vomiting during the course of the study may be deleted from the statistical analysis if vomiting occurred at or before 2 times median t_{max} of the reference product.

For subjects with pre-dose plasma concentrations, the subject's data may be included without any adjustments in all PK measurements and calculations if the pre-dose concentration is ≤ 5% of C_{max}. If the pre-dose value is > 5% of C_{max}, the subject's data may be dropped from all bioequivalence evaluations.

11.2.3. Safety Population

All subjects who received at least one dose of IP will be included in the safety analysis for the study.

11.3. Protocol Deviations and Changes to Planned Analyses

Permission from the sponsor in writing will be obtained should any changes be required to the CSP and a protocol amendment will be written. For protocol amendments, see Section 3.1. Should the safety of the subjects necessitate immediate action, which represents a deviation from the CSP, the sponsor, IEC and SAHPRA will be informed as soon as possible.

Protocol deviations and changes to planned analyses will be described in the CSR.

11.4. Pharmacokinetic Parameters

Calculation of the PK parameters will be made with Phoenix® WinNonlin® 8.1 (or higher) (Certara, L.P., 1699 South Hanley Road, St Louis, Missouri 63144, USA).

The PK parameters will be calculated for each subject and treatment using non-compartmental analysis and using the actual sampling time intervals (relative to IP administration).

11.4.1. Primary Pharmacokinetic Parameters for Haloperidol

- Maximum observed plasma concentration (C_{max})
- Area under the plasma concentration versus time curve, from time zero to t, where t is the time of the last quantifiable concentration ($AUC_{(0-t)}$)
- Area under the plasma concentration versus time curve, with extrapolation to infinity ($AUC_{(0-\infty)}$)

11.4.2. Secondary Pharmacokinetic Parameters for Haloperidol

- Time to maximum observed plasma concentration (t_{max})
- Terminal elimination rate constant (λ_z)
- Apparent terminal elimination half-life ($t_{½}$)

11.5. Safety Variables

Refer to Section 9.1.

11.5.1. Missing data for Adverse Events

Refer to SAP for details.

11.6. Outliers

For FDA submission, no outlier testing will apply.

11.7. Presentation of PK Data, Descriptive Statistics and PK Assessment

Refer to SAP for outputs presented.

The Day 1 pre-dose concentrations of haloperidol will be used for baseline. Where possible, the PK parameters will then be estimated on baseline subtracted plasma concentrations of haloperidol. Pharmacokinetic parameters will be calculated on the baseline subtracted concentrations (even if some values are negative, they are used for computing AUC as they are).

Source data shall be used in all derived PK parameter calculations without prior rounding.

The actual blood sampling times and time deviations will be listed for each subject dosed, product and scheduled sampling time. A listing reflecting summary statistics (number of subjects/observations [n], arithmetic mean, geometric mean, median, CV%, SD, minimum and maximum) per product will be provided for plasma concentrations of haloperidol.

Concentrations below the lower limit of quantification (LLOQ) will be indicated as below the limit of quantification (BLQ).

A listing reflecting summary statistics (n, arithmetic mean, geometric mean, geometric mean ratios, median, CV%, SD, minimum and maximum) per treatment will be provided for PK

parameters of haloperidol. For t_{max} only the median, minimum and maximum, and for $t_{½}$ the mean, median, minimum and maximum values will be presented.

The individual plasma haloperidol concentration versus actual time profiles for each subject and product, as well as the mean plasma (arithmetic and geometric) plasma haloperidol concentration versus scheduled time profiles for each product, will be presented graphically on a linear-linear and log-linear scale. Individual plasma concentrations will be presented using actual, rather than planned, sampling times. Combined individual concentration versus time graphs per product will also be presented on a linear-linear scale, together with the geometric mean values. The individual log-linear graphs reflecting the WinNonlin modeling results, will be presented using SAS.

The data listings, descriptive statistics, statistical analysis and graphs of this study will be generated using SAS/STAT® and SAS/GRAPH® software.

Refer to SAP for further details.

11.8. Analysis of Bioequivalence

The test product will be compared to the reference product by means of statistical analysis with respect to the primary PK parameters using an analysis of variance (ANOVA) with sequence, subject(sequence), product and period effects after logarithmic transformation of the data. Point estimates and 90% CIs for the "test/reference" geometric mean ratios of these parameters will be obtained by taking the antilog of the “test – reference” difference and will be tabulated.

Bioequivalence of the test and reference products will be assessed on the basis of the 90% CIs for estimates of the geometric mean ratios between the primary PK parameters of the test and reference products in relation to the conventional bioequivalence range of 80.00% to 125.00%.

A non-parametric Wilcoxon signed rank test may be performed on the variable t_{max} for the “test - reference” differences and the results will be tabulated.

Refer to SAP for further details.

11.9. Presentation of Baseline Characteristics and Safety Data

Baseline characteristics and safety data will be presented as indicated in the SAP. Data captured but not presented as listed or summarized data will be available in the CRFs or the source data capture system.

Demographic and anthropometric data will be listed for all subjects in the safety population. Demographic characteristics will be tabulated by treatment (n, mean, SD, minimum and maximum for age and BMI; and frequency counts and percentages for race, age groups and sex).

Adverse events will be coded, listed and summarized by treatment. Adverse events will be coded and summarized by System Organ Class (SOC) and preferred term and product; SOC, preferred term, causality and product; and SOC, preferred term, intensity and product. For the tabulations, AEs will be reported as either having a reasonable possibility ("Related") or as having no reasonable possibility of being related ("Not Related").

Hematology and clinical chemistry values will be listed and summarized (n, mean, SD, median, minimum, maximum), and urinalysis data will be listed for all subjects in the safety population. Abnormal hematology and clinical chemistry values will be flagged as "L" (for values lower than the lower limit of the reference range) and "H" (for values higher than the upper limit of the reference range). Clinical significance will be indicated as "NCS" (abnormal, not clinically significant) or "CS" (abnormal, clinically significant) or "Rep" (whether the test was repeated).

Vital signs and 12-lead ECG data will be listed and summarized (as appropriate) for all subjects in the safety population.

Prior and concomitant medication will be coded and listed separately.

12. ADVERSE EVENTS

Each subject will be carefully monitored by the investigator for AEs. In addition, information on AEs will be obtained from the subjects by study staff regularly questioning them, although no leading questions will be asked. When an AE occurs, the investigator will decide whether to withdraw the subject from the study and/or initiate appropriate treatment. After withdrawal from the study, it will be ensured that the subject is given appropriate medical care, if needed, which may take the form of referral to a physician.

In the case of any event requiring medical intervention occurring during the clinic stay, the investigator will institute general supportive measures including, where necessary, respiratory assistance and cardiopulmonary resuscitation.

12.1. Definitions

12.1.1. Adverse Events (or Adverse Experiences)

Any untoward medical occurrence in a patient or clinical investigation trial participant administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

12.1.2. Adverse Drug Reaction

A response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of diseases or for modification of physiological function. Response in this context means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility.

12.1.3. Unexpected Adverse Drug Reaction

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved IP or package insert/summary of product characteristics for an approved product).

12.1.4. Serious Adverse Events

Serious adverse event (SAE) means an adverse reaction which:

- Results in death,
- Is life-threatening,*

  * *Life-threatening in this context refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.*

- Requires in-patient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability or incapacity,
- Is a congenital anomaly or birth defect, or
- Other medically important condition.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse. Any suspected transmission via an IP or an infectious agent is also considered a serious adverse reaction.

12.2. Classification of Adverse Events

Adverse events have to be recorded on an AE form in the subject's CRF and graded as mild, moderate, or severe according to the following definitions:

- **Mild:** Causing no limitation of usual activities; the subject may experience slight discomfort.
- **Moderate:** Causing some limitation of usual activities, the subject may experience annoying discomfort.
- **Severe:** Causing inability to carry out usual activities, the subject may experience intolerable discomfort or pain.

12.3. Definition of Adverse Events Causality

The investigator will determine the relationship of any adverse event to the IP according to the following criteria:

- **Reasonable Possibility:** A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the treatment, which could or could not be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on treatment withdrawal, or for which information on treatment withdrawal may be lacking or unclear.
- **No Reasonable Possibility:** A clinical event, including laboratory test abnormality, either with a temporal relationship to treatment administration which makes a causal relationship improbable or which has little to no temporal relationship to treatment administration, and in which other drugs, chemicals or underlying disease provide plausible explanations.

12.4. Adverse Events Documentation

The recording of every single AE/SAE has to be in line with ICH Topic E2B (R3) and has to meet the following requirements:

- Detailed subject data
- Exact documentation of the event
- Exact description of temporal sequence to the therapy course
- Documentation of severity
- Documentation of the results of diagnostic and therapeutic measurements
- Results of a repeated exposure (re-exposure) if possible
- Details of the development and outcome including medical judgment
- As much data as possible have to be obtained which are important for judgment concerning the relationship of the AE/SAE to IP
- Critical examination of the relationship to IP

All AEs have to be charted according to this scheme when spontaneously reported by the subject, observed by the principal investigator or designee or elicited by general questioning.

12.5. Reporting Procedures of Adverse Events/Serious Adverse Events

The reporting of all AEs and SAEs will be according to FARMOVS SOPs.

The principal investigator or designee is responsible for recording in the CRF all AEs which have occurred from first administration of IP (including clinically important deviations of laboratory values from the reference ranges), regardless of their relationship to the IP. Any AE or SAE reported after the end of the study within a reasonable time period and considered to have been caused by the IP must also be recorded. All recorded AEs will be summarized and reported on in the CSR.

All suspected adverse reactions that occur in the concerned study, and that are both unexpected and serious are subject to expedited reporting. A suspected unexpected serious adverse reaction (SUSAR) which is fatal or life-threatening will be reported as soon as possible to the authority.

In the occurrence of **any** SAEs (including death, irrespective of the reason) the sponsor has to be notified **immediately** (within 24 hours) after becoming aware of the event. The minimum information that must be included in the immediate report is:

- An event meeting the criteria of SAE.
- A qualified reporter, defined as an investigator of this study or his/her delegate.
- A qualified subject, defined as a subject who has consented to this study.
- Suspected IP (test or reference), if initiated.
- The investigator's or delegate's causality assessment.
- The immediate report should be followed promptly by a detailed, written report.

The sponsor's contact person for reporting of SAEs is:

Sponsor Contact Person

In accordance with regulatory requirements, the IEC and the SAHPRA have to be notified as soon as possible but not later than within 15 days after becoming aware of the occurrence of any SAEs (including death, irrespective of the reason). In accordance with FARMOVS SOP, the monitor will also be notified.

The report should contain a detailed description of the observed symptoms and the concomitant therapy. The investigator has to judge the possible causal relationship between the event and the IP and should arrange additional examinations at his/her discretion to clarify if the event is connected with the IP. He/She should consult a specialist if necessary.

In the event of a pregnancy, the investigator should notify the sponsor within 24 hours of being informed about the pregnancy. Follow-up reports will be provided at appropriate intervals.

The sponsor's contact person for reporting of a pregnancy is:

Sponsor Contact Person

[redacted]

In accordance with regulatory requirements, the IEC and the SAHPRA have to be notified as soon as possible but not later than within 15 days after becoming aware of the pregnancy. In accordance with FARMOVS SOP, the monitor will also be notified.

All AEs and SAEs have to be followed up until an outcome is known. In the event of an SAE, the outcome has to be reported in the CRF, as well as to the principal investigator, sponsor, monitor, the IEC and the SAHPRA.

13. LEGAL AND ADMINISTRATIVE ASPECTS

13.1. Documentation

All source documents generated in connection with the study will be retained in the limited access file storage area, respecting the privacy and confidentiality of all records that could identify the subjects. Direct access is allowed only for authorized people for monitoring and auditing purposes. Source documents will be handled, stored and archived according to in-house procedures.

Investigator-specific essential documents will be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. These documents could be retained for a longer period however, in accordance with regulatory requirements or in agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator as to when these documents no longer need to be retained.

Study documentation will be archived by FARMOVS Bloemfontein for at least 15 years.

13.2. Publication of Results

If a publication (e.g., in a scientific journal) based on the results of this study is envisaged by FARMOVS, approval from the sponsor will be obtained and a draft manuscript will be submitted to the sponsor for scrutiny and comment. The choice of conduit will be mutually agreed on by the principal investigator and the sponsor.

13.3. Sponsor's Obligation

The onus rests with the sponsor to ensure that the CSP complies with all their requirements.

13.4. Clinical Study Report

An integrated CSR will be prepared in accordance with the standards of the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Copies of the CSR will be provided to the IEC and the SAHPRA in accordance with regulatory requirements and FARMOVS SOPs. In the event of premature termination of the study or other conditions specified in ICH E3, an abbreviated CSR may be prepared.

14. REFERENCES

1. Product Information. Haloperidol Tablets, USP. Mylan Pharmaceuticals Inc. Revised Nov 2016.

2. Drug Bank. https://www.drugbank.ca/drugs/DB00502. Accessed 26 July 2019.

3. Summary of Product Characteristics. Haloperidol 10 mg Tablets. TEVA UK Limited. Revised 08/03/2019.

4. Diletti E, Hauschke D, Steinijans VW. Sample Size Determination for Bioequivalence Assessment by Means of Confidence Intervals. Int J Clin Pharmacol Ther Toxicol. 1992; 30(Suppl 1): S51-8.

5. Yun MH, Kwon JT, Kwon K. Pharmacokinetics and bioequivalence of haloperidol tablet by liquid chromatographic mass spectrometry with electrospray ionization. Arch Pharm Res. 2005; 28(4): 488-492.

Guidance documentation referred to within the CSP include, but are not limited to the following:

- Declaration of Helsinki, World Medical Association, Fortaleza, Brazil, 2013
- Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa, Department of Health, South Africa, 2006
- International Council for Harmonisation (ICH) Harmonised Guideline, Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice (GCP) E6(R2), Step 5, dated 09 November 2016
- United States Department of Health and Human Services, Food and Drug Administration (FDA) Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations. Center for Drug Evaluation and Research (CDER) March 2003 BP
- United States Department of Health and Human Services, Food and Drug Administration (FDA) Guidance for Industry: Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA, Draft Guidance. Center for Drug Evaluation and Research (CDER), December 2013 Biopharmaceutics

- United States Department of Health and Human Services, Food and Drug Administration Guidance for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies, Center for Drug Evaluation and Research (CDER), December 2002 BP
- United States Department of Health and Human Services, FDA – Handling and Retention of BA and BE Testing Samples, CDER, May 2004
- United States Department of Health and Human Services, FDA – Statistical Approaches to Establishing Bioequivalence, CDER January 2001 BP
- International Council for Harmonisation (ICH), Guideline for Structure and Content of Clinical Study Reports (ICH E3), 1995
- ICH Topic E2B (R3) Electronic Transmission of Individual Case Safety Reports Implementation Guide — Data Elements and Message Specification

15. APPENDICES

15.1. Menu

The following table summarizes the recipe constituents for a high-fat, high-calorie breakfast:

Food	**Amount (g)**	**Energy (cal)**	**Carbohydrate (g)♦**	**Protein (g)**	**Fat (g)**
Tomato	50	10.59	2.0 (8.09 cal)	0.4 (1.62 cal)	0.1 (0.88 cal)
Butter	16	115.8	0.0	0.1 (0.40 cal)	13.1 (115.40 cal)
Milk – whole, fresh	200	124.66	9.6 (38.86 cal)	6.4 (25.9 cal)	6.8 (59.90 cal)
Potato croquette / chips fried in vegetable oil	50	152.21	19.3 (78.12 cal)	2.2 (8.90 cal)	7.4 (65.19 cal)
Omelette – plain, using whole milk and butter / margarine	120	180.74	2.3 (9.31 cal)	12.1 (48.98 cal)	13.9 (122.45 cal)
Bacon with fat (fried with 2 teaspoons of vegetable oil)	40	223.74	0.2 (0.81 cal)	12.2 (49.38 cal)	19.7 (173.55 cal)
Bread rolls – whole wheat white	50	131.38	26.2 (106.05 cal)	4.3 (17.40 cal)	0.9 (7.93 cal)
TOTAL		939.15	59.6 g (241.24 cal)	37.7 g (152.60 cal)	61.9 g (545.31 cal)
Energy (cal) per FDA requirements		800-1000	250	150	500-600

♦ Carbohydrate value includes fiber.

Data Source: T D D Dietetics, Life Rosepark Hospital, 56 Gustav Crescent, Bloemfontein 9301, South Africa.

15.2. Subject Discharge Declaration

DECLARATION / VERKLARING

(A copy of this is retained by the subject)

I / Ek,

_____

(Full names and surname / Volle name en van)

Hereby declare that I will not drive a motorized vehicle, operate any machinery or perform any hazardous task for a further 24 hours after discharge from the study center. Any questions concerning the above have been discussed with the registered nurse. / Verklaar hiermee dat ek vir 24 uur na ontslag nie ‘n voertuig sal bestuur, enige masjinerie sal gebruik of enige gevaarlike taak sal uitvoer nie. Vrae in verband hiermee is reeds met die geregistreerde verpleegkundige uitgeklaar.

Signature of Subject / Handtekening van Deelnemer	**Date / Datum**
Signature of Registered Nurse or Designee	**Date**

15.3. Product Information – Reference Product

HALOPERIDOL- haloperidol tablet
Mylan Pharmaceuticals Inc.
Reference Label Set Id: 405ee4c4-394c-47df-a6ec-9b4f4e7ca768

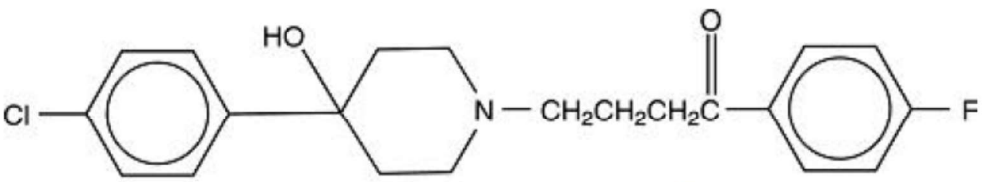
WARNING

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. Haloperidol is not approved for the treatment of patients with dementia-related psychosis (see WARNINGS).

DESCRIPTION

Haloperidol is the first of the butyrophenone series of major tranquilizers. The chemical designation is 4-[4-(p-chloro-phenyl)-4-hydroxypiperidino]-4' fluorobutyrophenone and it has the following structural formula:



$C_{21}H_{23}ClFNO_2$ 375.87

Haloperidol is supplied as tablets for oral administration containing 0.5 mg, 1 mg, 2 mg, 5 mg, 10 mg or 20 mg of haloperidol, USP and contains the following inactive ingredients: colloidal silicon dioxide, FD&C Yellow No. 6 Aluminum Lake, magnesium stearate, microcrystalline cellulose, pregelatinized starch and sodium lauryl sulfate. In addition, the 10 mg and 20 mg tablets also contain FD&C Blue No. 1 Aluminum Lake.

CLINICAL PHARMACOLOGY

The precise mechanism of action has not been clearly established.

INDICATIONS AND USAGE

Haloperidol tablets are indicated for use in the management of manifestations of psychotic disorders.

Haloperidol tablets are indicated for the control of tics and vocal utterances of Tourette's Disorder in children and adults. Haloperidol tablets are effective for the treatment of severe behavior problems in

children of combative, explosive hyperexcitability (which cannot be accounted for by immediate provocation). Haloperidol tablets are also effective in the short-term treatment of hyperactive children who show excessive motor activity with accompanying conduct disorders consisting of some or all of the following symptoms: impulsivity, difficulty sustaining attention, aggressivity, mood lability, and poor frustration tolerance. Haloperidol tablets should be reserved for these two groups of children only after failure to respond to psychotherapy or medications other than antipsychotics.

CONTRAINDICATIONS

Haloperidol tablets are contraindicated in severe toxic central nervous system depression or comatose states from any cause and in individuals who are hypersensitive to this drug or have Parkinson's disease.

WARNINGS

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Haloperidol is not approved for the treatment of patients with dementia-related psychosis (see BOXED WARNING).

Cardiovascular Effects

Cases of sudden death, QT-prolongation, and Torsades de pointes have been reported in patients receiving haloperidol. Higher than recommended doses of any formulation of haloperidol appear to be associated with a higher risk of QT-prolongation and Torsades de pointes. Although cases have been reported even in the absence of predisposing factors, particular caution is advised in treating patients with other QT-prolonging conditions (including electrolyte imbalance [particularly hypokalemia and hypomagnesemia], drugs known to prolong QT, underlying cardiac abnormalities, hypothyroidism, and familial long QT-syndrome).

Tardive Dyskinesia

A syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, antipsychotic drugs should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that, 1) is known to respond to antipsychotic drugs, and, 2) for whom alternative, equally effective, but potentially less harmful treatments are **not** available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for

continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome. (For further information about the description of tardive dyskinesia and its clinical detection, please refer to ADVERSE REACTIONS.)

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Hyperpyrexia and heat stroke, not associated with the above symptom complex, have also been reported with haloperidol.

Falls

Haloperidol tablets may cause somnolence, postural hypotension, motor and sensory instability, which may lead to falls and, consequently, fractures or other injuries. For patients with diseases, conditions, or medications that could exacerbate these effects, complete fall risk assessments when initiating antipsychotic treatment and recurrently for patients on long-term antipsychotic therapy.

Usage in Pregnancy

Pregnancy

Nonteratogenic Effects

Neonates exposed to antipsychotic drugs, during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization.

Haloperidol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Rodents given 2 to 20 times the usual maximum human dose of haloperidol by oral or parenteral routes showed an increase in incidence of resorption, reduced fertility, delayed delivery and pup mortality. No

teratogenic effect has been reported in rats, rabbits or dogs at dosages within this range, but cleft palate has been observed in mice given 15 times the usual maximum human does. Cleft palate in mice appears to be a nonspecific response to stress or nutritional imbalance as well as to a variety of drugs, and there is no evidence to relate this phenomenon to predictable human risk for most of these agents.

There are no well controlled studies with haloperidol in pregnant women. There are reports, however, of cases of limb malformations observed following maternal use of haloperidol along with other drugs which have suspected teratogenic potential during the first trimester of pregnancy. Causal relationships were not established in these cases. Since such experience does not exclude the possibility of fetal damage due to haloperidol, this drug should be used during pregnancy or in women likely to become pregnant only if the benefit clearly justifies a potential risk to the fetus. Infants should not be nursed during drug treatment.

Combined Use of Haloperidol and Lithium

An encephalopathic syndrome (characterized by weakness, lethargy, fever, tremulousness and confusion, extrapyramidal symptoms, leukocytosis, elevated serum enzymes, BUN, and FBS) followed by irreversible brain damage has occurred in a few patients treated with lithium plus haloperidol. A causal relationship between these events and the concomitant administration of lithium and haloperidol has not been established; however, patients receiving such combined therapy should be monitored closely for early evidence of neurological toxicity and treatment discontinued promptly if such signs appear.

General

A number of cases of bronchopneumonia, some fatal, have followed the use of antipsychotic drugs, including haloperidol. It has been postulated that lethargy and decreased sensation of thirst due to central inhibition may lead to dehydration, hemoconcentration and reduced pulmonary ventilation. Therefore, if the above signs and symptoms appear, especially in the elderly, the physician should institute remedial therapy promptly.

Although not reported with haloperidol, decreased serum cholesterol and/or cutaneous and ocular changes have been reported in patients receiving chemically-related drugs.

Haloperidol may impair the mental and/or physical abilities required for the performance of hazardous tasks such as operating machinery or driving a motor vehicle. The ambulatory patient should be warned accordingly.

The use of alcohol with this drug should be avoided due to possible additive effects and hypotension.

PRECAUTIONS

Leukopenia, Neutropenia and Agranulocytosis

In clinical trial and post-marketing experience, events of leukopenia/neutropenia have been reported temporally related to antipsychotic agents, including haloperidol. Agranulocytosis (including fatal cases) has also been reported.

Possible risk factors for leukopenia/neutropenia include preexisting low white blood cell count (WBC) and history of drug induced leukopenia/neutropenia. Patients with a preexisting low WBC or a history of drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and should discontinue haloperidol at the first sign of a decline in WBC in the absence of other causative factors.

Patients with neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count < 1,000/mm^3) should discontinue haloperidol and have their WBC followed until recovery.

Haloperidol should be administered cautiously to patients:

-with severe cardiovascular disorders, because of the possibility of transient hypotension and/or precipitation of anginal pain. Should hypotension occur and a vasopressor be required, epinephrine should not be used since haloperidol may block its vasopressor activity and paradoxical further lowering of the blood pressure may occur. Instead, metaraminol, phenylephrine or norepinephrine should be used.

-receiving anticonvulsant medications, with a history of seizures, or with EEG abnormalities, because haloperidol may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be concomitantly maintained.

-with known allergies, or with a history of allergic reactions to drugs.

-receiving anticoagulants, since an isolated instance of interference occurred with the effects of one anticoagulant (phenindione).

If concomitant antiparkinson medication is required, it may have to be continued after haloperidol is discontinued because of the difference in excretion rates. If both are discontinued simultaneously, extrapyramidal symptoms may occur. The physician should keep in mind the possible increase in intraocular pressure when anticholinergic drugs, including antiparkinson agents, are administered concomitantly with haloperidol.

As with other antipsychotic agents, it should be noted that haloperidol may be capable of potentiating CNS depressants such as anesthetics, opiates, and alcohol.

In a study of 12 schizophrenic patients coadministered haloperidol and rifampin, plasma haloperidol levels were decreased by a mean of 70% and mean scores on the Brief Psychiatric Rating Scale were increased from baseline. In five other schizophrenic patients treated with haloperidol and rifampin, discontinuation of rifampin produced a mean 3.3-fold increase in haloperidol concentrations. Thus, careful monitoring of clinical status is warranted when rifampin is administered or discontinued in haloperidol-treated patients.

When haloperidol is used to control mania in cyclic disorders, there may be a rapid mood swing to depression. Severe neurotoxicity (rigidity, inability to walk or talk) may occur in patients with thyrotoxicosis who are also receiving antipsychotic medication, including haloperidol.

No mutagenic potential of haloperidol was found in the Ames Salmonella microsomal activation assay. Negative or inconsistent positive findings have been obtained in *in vitro* and *in vivo* studies of effects of haloperidol on chromosome structure and number. The available cytogenetic evidence is considered too inconsistent to be conclusive at this time.

Carcinogenicity studies using oral haloperidol were conducted in Wistar rats (dosed at up to 5 mg/kg daily for 24 months) and in Albino Swiss mice (dosed at up to 5 mg/kg daily for 18 months). In the rat study, survival was less than optimal in all dose groups, reducing the number of rats at risk for developing tumors. However, although a relatively greater number of rats survived to the end of the study in high dose male and female groups, these animals did not have a greater incidence of tumors than control animals. Therefore, although not optimal, this study does suggest the absence of a haloperidol related increase in the incidence of neoplasia in rats at doses up to 20 times the usual daily human dose for chronic or resistant patients.

In female mice at 5 and 20 times the highest initial daily dose for chronic or resistant patients, there was a statistically significant increase in mammary gland neoplasia and total tumor incidence; at 20 times the same daily dose there was a statistically significant increase in pituitary gland neoplasia. In male mice, no statistically significant differences in incidences of total tumors or specific tumor types were noted.

Antipsychotic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro,* a factor of potential importance if the prescription of these drugs is contemplated in a

patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of antipsychotic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

There are no well controlled studies with haloperidol in pregnant women. There are reports, however, of cases of limb malformations observed following maternal use of haloperidol along with other drugs which have suspected teratogenic potential during the first trimester of pregnancy. Causal relationships were not established in these cases. Since such experience does not exclude the possibility of fetal damage due to haloperidol, this drug should be used during pregnancy or in women likely to become pregnant only if the benefit clearly justifies a potential risk to the fetus. Infants should not be nursed during drug treatment.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical studies of haloperidol did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not consistently identified differences in responses between the elderly and younger patients. However, the prevalence of tardive dyskinesia appears to be highest among the elderly, especially elderly women (see WARNINGS: Tardive Dyskinesia). Also, the pharmacokinetics of haloperidol in geriatric patients generally warrants the use of lower doses (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Cardiovascular Effects

Tachycardia, hypotension, and hypertension have been reported. QT prolongation and/or ventricular arrhythmias have also been reported, in addition to ECG pattern changes compatible with the polymorphous configuration of Torsades de pointes, and may occur more frequently with high doses and in predisposed patients (see WARNINGS and PRECAUTIONS).

Cases of sudden and unexpected death have been reported in association with the administration of haloperidol. The nature of the evidence makes it impossible to determine definitively what role, if any, haloperidol played in the outcome of the reported cases. The possibility that haloperidol caused death cannot, of course, be excluded, but it is to be kept in mind that sudden and unexpected death may occur in psychotic patients when they go untreated or when they are treated with other antipsychotic drugs.

CNS Effects

Extrapyramidal Symptoms (EPS)

EPS during the administration of haloperidol have been reported frequently, often during the first few days of treatment. EPS can be categorized generally as Parkinson-like symptoms, akathisia, or dystonia (including opisthotonos and oculogyric crisis). While all can occur at relatively low doses, they occur more frequently and with greater severity at higher doses. The symptoms may be controlled with dose reductions or administration of antiparkinson drugs such as benztropine mesylate, USP or trihexyphenidyl hydrochloride, USP. It should be noted that persistent EPS have been reported; the drug may have to be discontinued in such cases.

Dystonia

Class Effect

Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

Withdrawal Emergent Neurological Signs

Generally, patients receiving short-term therapy experience no problems with abrupt discontinuation of antipsychotic drugs. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain of these cases the dyskinetic movements are indistinguishable from the syndrome described below under “Tardive Dyskinesia” except for duration. It is not known whether gradual withdrawal of antipsychotic drugs will reduce the rate of occurrence of withdrawal emergent neurological signs but until further evidence becomes available, it seems reasonable to gradually withdraw use of haloperidol.

Tardive Dyskinesia

As with all antipsychotic agents, haloperidol has been associated with persistent dyskinesias. Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high dose therapy, especially females. The symptoms are persistent and in some patients appear irreversible. The syndrome is characterized by rhythmical involuntary movements of tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities and the trunk.

There is no known effective treatment for tardive dyskinesia; antiparkinson agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, this syndrome may be masked.

It has been reported that fine vermicular movement of the tongue may be an early sign of tardive dyskinesia and if the medication is stopped at that time, the full syndrome may not develop.

Tardive Dystonia

Tardive dystonia, not associated with the above syndrome, has also been reported. Tardive dystonia is characterized by delayed onset of choreic or dystonic movements, is often persistent, and has the potential of becoming irreversible.

Other CNS Effects

Insomnia, restlessness, anxiety, euphoria, agitation, drowsiness, depression, lethargy, headache, confusion, vertigo, grand mal seizures, exacerbation of psychotic symptoms including hallucinations and catatonic-like behavioral states which may be responsive to drug withdrawal and/or treatment with anticholinergic drugs.

Body as a Whole: Neuroleptic malignant syndrome (NMS), hyperpyrexia and heat stroke have been reported with haloperidol. (See WARNINGS for further information concerning NMS.)

Hematologic Effects: Reports have appeared citing the occurrence of mild and usually transient leukopenia and leukocytosis, minimal decreases in red blood cell counts, anemia, or a tendency toward

lymphomonocytosis. Agranulocytosis has rarely been reported to have occurred with the use of haloperidol, and then only in association with other medication.

Liver Effects: Impaired liver function and/or jaundice have been reported.

Dermatologic Reactions: Maculopapular and acneiform skin reactions and isolated cases of photosensitivity and loss of hair.

Endocrine Disorders: Lactation, breast engorgement, mastalgia, menstrual irregularities, gynecomastia, impotence, increased libido, hyperglycemia, hypoglycemia and hyponatremia.

Gastrointestinal Effects: Anorexia, constipation, diarrhea, hypersalivation, dyspepsia, nausea and vomiting.

Autonomic Reactions: Dry mouth, blurred vision, urinary retention, diaphoresis and priapism.

Respiratory Effects: Laryngospasm, bronchospasm and increased depth of respiration.

Special Senses: Cataracts, retinopathy and visual disturbances.

Post-marketing Events

Hyperammonemia has been reported in a 5½ year old child with citrullinemia, an inherited disorder of ammonia excretion, following treatment with haloperidol.

OVERDOSAGE

Manifestations

In general, the symptoms of overdosage would be an exaggeration of known pharmacologic effects and adverse reactions, the most prominent of which would be: 1) severe extrapyramidal reactions, 2) hypotension, or 3) sedation. The patient would appear comatose with respiratory depression and hypotension which could be severe enough to produce a shock-like state. The extrapyramidal reaction would be manifest by muscular weakness or rigidity and a generalized or localized tremor as demonstrated by the akinetic or agitans types respectively. With accidental overdosage, hypertension rather than hypotension occurred in a 2 year old child. The risk of ECG changes associated with Torsades de pointes should be considered. (For further information regarding Torsades de pointes, please refer to ADVERSE REACTIONS.)

Treatment

Gastric lavage or induction of emesis should be carried out immediately followed by administration of activated charcoal. Since there is no specific antidote, treatment is primarily supportive. A patent airway must be established by use of an oropharyngeal airway or endotracheal tube or, in prolonged cases of coma, by tracheostomy. Respiratory depression may be counteracted by artificial respiration and mechanical respirators. Hypotension and circulatory collapse may be counteracted by use of intravenous fluids, plasma, or concentrated albumin, and vasopressor agents such as metaraminol, phenylephrine and norepinephrine. Epinephrine should not be used. In case of severe extrapyramidal reactions, antiparkinson medication should be administered. ECG and vital signs should be monitored especially for signs of Q-T prolongation or dysrhythmias and monitoring should continue until the ECG is normal. Severe arrhythmias should be treated with appropriate antiarrhythmic measures.

DOSAGE AND ADMINISTRATION

There is considerable variation from patient to patient in the amount of medication required for treatment. As with all antipsychotic drugs, dosage should be individualized according to the needs and response of each patient. Dosage adjustments, either upward or downward, should be carried out as rapidly as practicable to achieve optimum therapeutic control.

To determine the initial dosage, consideration should be given to the patient's age, severity of illness, previous response to other antipsychotic drugs, and any concomitant medication or disease state. Children, debilitated or geriatric patients, as well as those with a history of adverse reactions to antipsychotic drugs, may require less haloperidol. The optimal response in such patients is usually obtained with more gradual dosage adjustments and at lower dosage levels, as recommended below.

Clinical experience suggests the following recommendations:

Oral Administration

Initial Dosage Range

Adults

Moderate Symptomatology - 0.5 mg to 2 mg b.i.d. or t.i.d.

Severe Symptomatology - 3 mg to 5 mg b.i.d. or t.i.d.

To achieve prompt control, higher doses may be required in some cases.

Geriatric or Debilitated Patients - 0.5 mg to 2 mg b.i.d. or t.i.d.

Chronic or Resistant Patients - 3 mg to 5 mg b.i.d. or t.i.d.

Patients who remain severely disturbed or inadequately controlled may require dosage adjustment. Daily dosages up to 100 mg may be necessary in some cases to achieve an optimal response. Infrequently haloperidol has been used in doses above 100 mg for severely resistant patients; however the limited clinical usage has not demonstrated the safety of prolonged administration of such doses.

Children

The following recommendations apply to children between the ages of 3 and 12 years (weight range 15 kg to 40 kg). Haloperidol is not intended for children under 3 years old. Therapy should begin at the lowest dose possible (0.5 mg per day). If required, the dose should be increased by an increment of 0.5 mg at 5 to 7 day intervals until the desired therapeutic effect is obtained. (See chart below.)

The total dose may be divided, to be given b.i.d. or t.i.d.

Psychotic Disorders - 0.05 mg/kg/day to 0.15 mg/kg/day

Nonpsychotic Behavior Disorders and Tourette's Disorder - 0.05 mg/kg/day to 0.075 mg/kg/day

Severely disturbed psychotic children may require higher doses. In severely disturbed, non-psychotic children or in hyperactive children with accompanying conduct disorders, who have failed to respond to psychotherapy or medications other than antipsychotics, it should be noted that since these behaviors may be short lived, short term administration of haloperidol may suffice. There is no evidence establishing a maximum effective dosage. There is little evidence that behavior improvement is further enhanced in dosages beyond 6 mg per day.

Maintenance Dosage

Upon achieving a satisfactory therapeutic response, dosage should then be gradually reduced to the

lowest effective maintenance level.

Switchover Procedure

The oral form should supplant the injectable as soon as practicable. In the absence of bioavailability studies establishing bioequivalence between these two dosage forms the following guidelines for dosage are suggested. For an initial approximation of the total daily dose required, the parenteral dose administered in the preceding 24 hours may be used. Since this dose is only an initial estimate, it is recommended that careful monitoring of clinical signs and symptoms, including clinical efficacy, sedation, and adverse effects, be carried out periodically for the first several days following the initiation of switchover. In this way, dosage adjustments, either upward or downward, can be quickly accomplished. Depending on the patient's clinical status, the first oral dose should be given within 12 to 24 hours following the last parenteral dose.

HOW SUPPLIED

Haloperidol Tablets, USP are available containing 0.5 mg, 1 mg, 2 mg, 5 mg, 10 mg or 20 mg of haloperidol, USP.

The 0.5 mg tablets are orange round tablets debossed with **MYLAN** over **351** on one side of the tablet and scored on the other side. They are available as follows:

NDC 0378-0351-01
bottles of 100 tablets

NDC 0378-0351-10
bottles of 1000 tablets

The 1 mg tablets are orange round tablets debossed with **MYLAN** over **257** on one side of the tablet and scored on the other side. They are available as follows:

NDC 0378-0257-01
bottles of 100 tablets

NDC 0378-0257-10
bottles of 1000 tablets

The 2 mg tablets are orange round tablets debossed with **MYLAN** over **214** on one side of the tablet and scored on the other side. They are available as follows:

NDC 0378-0214-01
bottles of 100 tablets

NDC 0378-0214-10
bottles of 1000 tablets

The 5 mg tablets are orange round tablets debossed with **MYLAN** over **327** on one side of the tablet and scored on the other side. They are available as follows:

NDC 0378-0327-01
bottles of 100 tablets

NDC 0378-0327-10
bottles of 1000 tablets

The 10 mg tablets are light green round tablets debossed with **MYLAN** over **334** on one side of the tablet and scored on the other side. They are available as follows:

NDC 0378-0334-01
bottles of 100 tablets

The 20 mg tablets are light blue round tablets debossed with **MYLAN** over **335** on one side of the

tablet and scored on the other side. They are available as follows:

NDC 0378-0335-01
bottles of 100 tablets

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

Protect from light.

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

Revised: 11/2016
HALO:R22

PRINCIPAL DISPLAY PANEL - 0.5 mg

NDC 0378-0351-01

Haloperidol
Tablets, USP
0.5 mg

Rx only 100 Tablets

Each tablet contains:
Haloperidol, USP 0.5 mg

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Keep container tightly closed.

Keep this and all medication out of the reach of children.

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

Protect from light.

Usual Dosage: See accompanying prescribing information.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

Mylan.com

RM0351A9

PRINCIPAL DISPLAY PANEL - 1 mg

NDC 0378-0257-01

Haloperidol
Tablets, USP
1 mg

Rx only 100 Tablets

Each tablet contains:
Haloperidol, USP 1 mg

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Keep container tightly closed.

Keep this and all medication out of the reach of children.

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

Protect from light.

Usual Dosage: See accompanying prescribing information.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

Mylan.com

RM0257A11

PRINCIPAL DISPLAY PANEL - 2 mg

NDC 0378-0214-01

Haloperidol
Tablets, USP
2 mg

Rx only 100 Tablets

Each tablet contains:
Haloperidol, USP 2 mg

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Keep container tightly closed.

Keep this and all medication out of the reach of children.

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

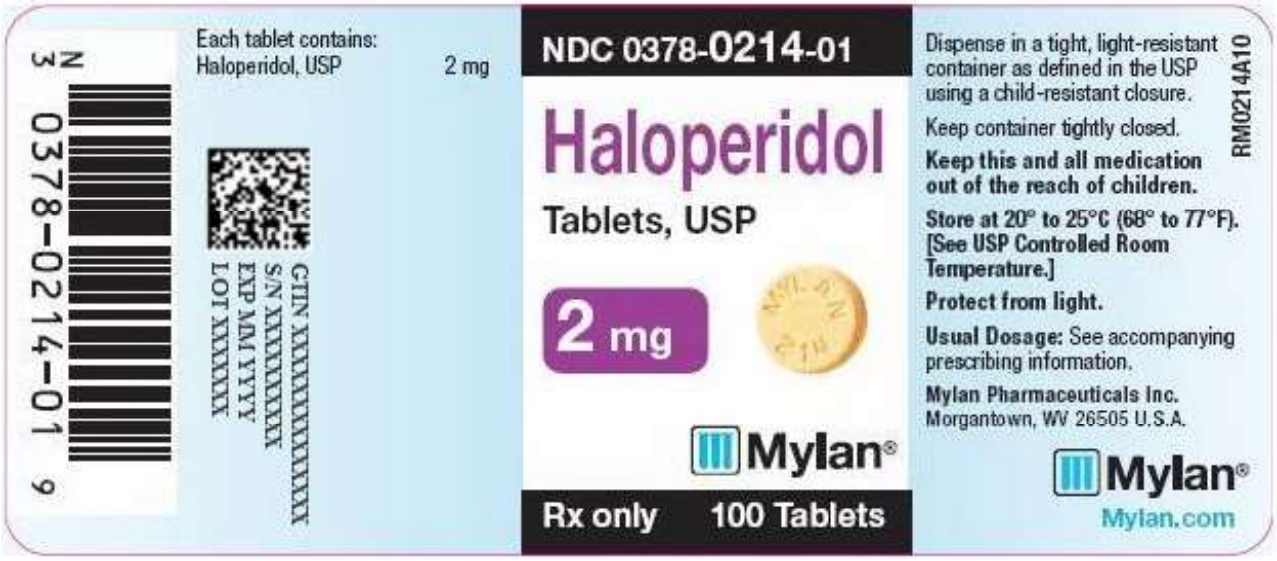
Protect from light.

Usual Dosage: See accompanying prescribing information.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

Mylan.com

RM0214A10



PRINCIPAL DISPLAY PANEL - 5 mg

NDC 0378-0327-01

Haloperidol
Tablets, USP
5 mg

Rx only 100 Tablets

Each tablet contains:
Haloperidol, USP 5 mg

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Keep container tightly closed.

Keep this and all medication out of the reach of children.

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

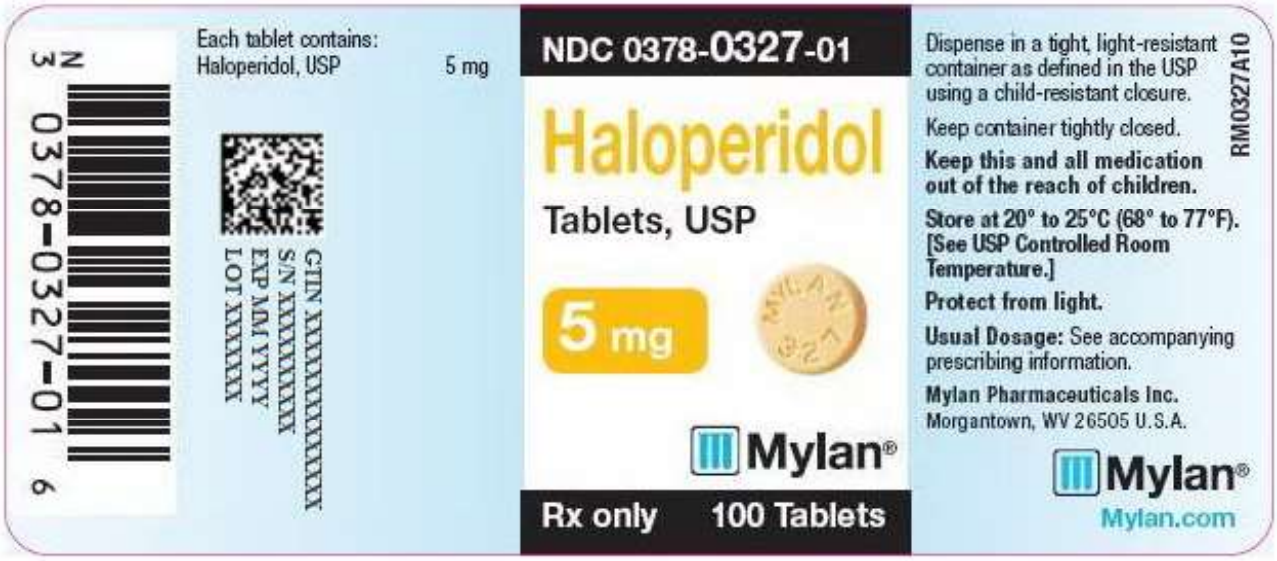
Protect from light.

Usual Dosage: See accompanying prescribing information.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

Mylan.com

RM0327A10



PRINCIPAL DISPLAY PANEL - 10 mg

NDC 0378-0334-01

Haloperidol
Tablets, USP
10 mg

Rx only 100 Tablets

Each tablet contains:
Haloperidol, USP 10 mg

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Keep container tightly closed.

Keep this and all medication out of the reach of children.

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

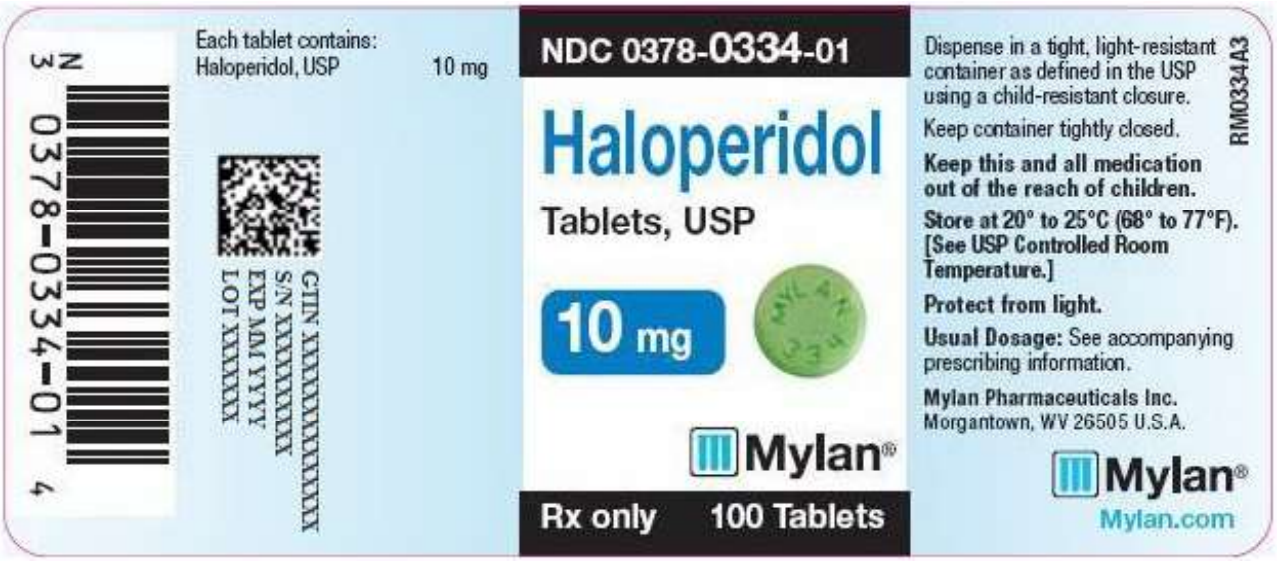
Protect from light.

Usual Dosage: See accompanying prescribing information.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

Mylan.com

RM0334A3



PRINCIPAL DISPLAY PANEL - 20 mg

NDC 0378-0335-01

Haloperidol
Tablets, USP
20 mg

Rx only 100 Tablets

Each tablet contains:
Haloperidol, USP 20 mg

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Keep container tightly closed.

Keep this and all medication out of the reach of children.

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

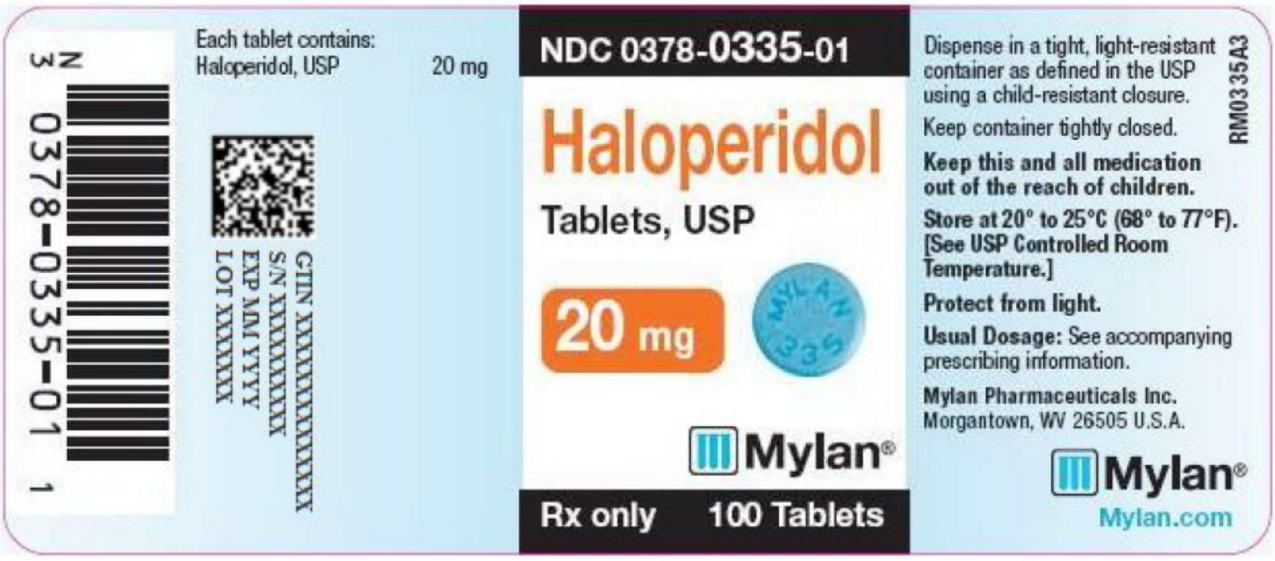
Protect from light.

Usual Dosage: See accompanying prescribing information.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

Mylan.com

RM0335A3



HALOPERIDOL

haloperidol tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0378 0351
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
HALOPERIDOL (UNII: J6292F8L3D) (HALOPERIDOL UNII:J6292F8L3D)	HALOPERIDOL	0.5 mg

Inactive Ingredients	
Ingredient Name	**Strength**
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
STARCH, CORN (UNII: O8232NY3SJ)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	

Product Characteristics			
Color	ORANGE	**Score**	2 pieces
Shape	ROUND	**Size**	6mm
Flavor		**Imprint Code**	MYLAN;351
Contains			

Packaging			
		Marketing Start	Marketing End

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0378 0351 01	100 in 1 BOTTLE, PLASTIC; Type 0: No a Combina ion Produc	06/10/1986	
2	NDC:0378 0351 10	1000 in 1 BOTTLE, PLASTIC; Type 0: No a Combina ion Produc	06/10/1986	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA070278	06/10/1986	

HALOPERIDOL

haloperidol tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0378 0257
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
HALOPERIDOL (UNII: J6292F8L3D) (HALOPERIDOL UNII:J6292F8L3D)	HALOPERIDOL	1 mg

Inactive Ingredients

Ingredient Name	Strength
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
STARCH, CORN (UNII: O8232NY3SJ)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	

Product Characteristics

Color	ORANGE	**Score**	2 pieces
Shape	ROUND	**Size**	7mm
Flavor		**Imprint Code**	MYLAN;257
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0378 0257 01	100 in 1 BOTTLE, PLASTIC; Type 0: No a Combina ion Produc	06/10/1986	

2	NDC:0378 0257 10	1000 in 1 BOTTLE, PLASTIC; Type 0: No a Combina ion Produc	06/10/1986	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA070278	06/10/1986	

HALOPERIDOL

haloperidol tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0378 0214
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
HALOPERIDOL (UNII: J6292F8L3D) (HALOPERIDOL UNII:J6292F8L3D)	HALOPERIDOL	2 mg

Inactive Ingredients

Ingredient Name	Strength
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
STARCH, CORN (UNII: O8232NY3SJ)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	

Product Characteristics

Color	ORANGE	**Score**	2 pieces
Shape	ROUND	**Size**	8mm
Flavor		**Imprint Code**	MYLAN;214
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0378 0214 01	100 in 1 BOTTLE, PLASTIC; Type 0: No a Combina ion Produc	06/10/1986	
2	NDC:0378 0214 10	1000 in 1 BOTTLE, PLASTIC; Type 0: No a Combina ion Produc	06/10/1986	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA070278	06/10/1986	

HALOPERIDOL

haloperidol tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0378 0327
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
HALOPERIDOL (UNII: J6292F8L3D) (HALOPERIDOL UNII:J6292F8L3D)	HALOPERIDOL	5 mg

Inactive Ingredients

Ingredient Name	Strength
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
STARCH, CORN (UNII: O8232NY3SJ)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	

Product Characteristics

Color	ORANGE	**Score**	2 pieces
Shape	ROUND	**Size**	9mm
Flavor		**Imprint Code**	MYLAN;327
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0378 0327 01	100 in 1 BOTTLE, PLASTIC; Type 0: No a Combina ion Produc	06/10/1986	
2	NDC:0378 0327 10	1000 in 1 BOTTLE, PLASTIC; Type 0: No a Combina ion Produc	06/10/1986	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA070278	06/10/1986	

HALOPERIDOL

haloperidol tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0378 0334
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
HALOPERIDOL (UNII: J6292F8L3D) (HALOPERIDOL UNII:J6292F8L3D)	HALOPERIDOL	10 mg

Inactive Ingredients	
Ingredient Name	**Strength**
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
STARCH, CORN (UNII: O8232NY3SJ)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	

Product Characteristics			
Color	GREEN (ligh green)	**Score**	2 pieces
Shape	ROUND	**Size**	9mm
Flavor		**Imprint Code**	MYLAN;334
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:0378 0334 01	100 in 1 BOTTLE, PLASTIC; Type 0: No a Combina ion Produc	07/17/2009	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA070278	07/17/2009	

HALOPERIDOL

haloperidol tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0378 0335
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
HALOPERIDOL (UNII: J6292F8L3D) (HALOPERIDOL UNII:J6292F8L3D)	HALOPERIDOL	20 mg

Inactive Ingredients

Ingredient Name	Strength
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
STARCH, CORN (UNII: O8232NY3SJ)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	

Product Characteristics

Color	BLUE (ligh blue)	**Score**	2 pieces
Shape	ROUND	**Size**	9mm
Flavor		**Imprint Code**	MYLAN;335
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0378 0335 01	100 in 1 BOTTLE, PLASTIC; Type 0: No a Combina ion Produc	07/17/2009	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA070278	07/17/2009	

Labeler - Mylan Pharmaceuticals Inc. (059295980)

Revised: 11/2016 Mylan Pharmaceuticals Inc.